TYPHOID FEVER

CLINICAL AND ANTIBIOTIC SENSITIVITY PROFILE

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DECLARATION

I solemnly declare that the dissertation titled **"TYPHOID FEVER – CLINICAL AND ANTIBIOTIC SENSITIVITY PROFILE"** was done by me at Coimbatore Medical College Hospital during the period from January 2004 – December 2005 under the guidance and supervision of Professor Dr. M. Shanmugam, M.D.

This dissertation is submitted to the Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of the requirement for the award of M.D. Degree (Branch – I) in General Medicine.

Place:

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CERTIFICATE

This is to certify that the enclosed work **"TYPHOID FEVER – CLINICAL AND ANTIBIOTIC SENSITIVITY PROFILE"** submitted by Dr. C. SELVARAJ to the Tamilnadu Dr. M.G.R. Medical University is based on bonafide cases studied and analysed by the candidate at the Department of Medicine, Coimbatore Medical College Hospital during the period from January 2004-December 2005 under my guidance and supervision and the conclusions reached in this study are his own.

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LIST OF ABBREVIATIONS

1.	ARDS	Acute Respiratory Distress Syndrome
2.	D I C	Disseminated Intravascular Coagulation
3.	C I E	Counter Immuno Elecrophoresis
4.	C M I	Cell Mediated Immunity
5.	E L I S A	Enzyme Linked Immunosorbent Assay
6.	F D P	Fibrin Degradation Products
7.	H I V	Human Immunodeficiency Virus
8.	L F T	Liver Function Tests
9.	M D R T F	Multi Drug Resistant Typhoid Fever
10.	P A N	Polyarteritis Nodosa
11.	P T	Prothrombin Time
12.	P T T	Partial Thromboplastin Time
13.	S A B E	Subacute Bacterial Endocarditis
14.	S G O T	Serum Glutamate Oxaloacetate Transaminase
15.	S G P T	Serum Glutamate Pyruvate Transaminase
16.	S L E	Systemic Lupus Erythematosus

INTRODUCTION

Typhoid fever is an unique human systemic infection known to medical science, since the days of Hippocrates though its clear differentiation from typhus fever was made only by the end of the 18th Century[1]. Though the advent of new antibiotics especially the chloramphenicol has dramatised the final outcome of the disease, the clinical pattern by which enteric fever can present is still diverse.

With better understanding of the causative organisms, their epidemiology and culture methods, other forms of presentation are also added in the modern literature. To list a few, Typhoid fever presenting as hepatitis, with bleeding manifestations, splenic abscesses[2], abscess in tibia, femur and rib, subcutaneous abscess[3], urinary tract infection, infective endocarditis, myelopathy, cerebellar ataxia[4],convulsions, schizophrenia, psychosis, Guillain barre syndrome[5], Osteomyelitis[6], Intravascular Haemolysis, Glomerulonephritis[7], Myocarditis have been reported. A physician therefore would be wise to have a clinical suspicion of typhoid fever in any case of fever of more than a few days duration whatever be the other manifestations.

Typhoid fever is still an important public health problem or endemic in many parts of India and in many other developing countries. It is difficult to estimate its real global impact due to problems related to clinical and laboratory diagnosis and since most of the cases are being treated outside the hospital and there is no reliable information about the incidence in our country.

The disease is transmitted mainly through the faeco-oral route. Other modes of transmission are also reported but they are rare. The disease is found to be endemic where sanitation is poor, where sewage disposal is improper and water supply is unprotected[8]. In Western Countries the outbreaks of the disease occur through carriers of the disease or after return from places where the disease is endemic, the so called holiday typhoid[9]. Such epidemics are usually rare in our country because the people have developed some degrees of immunity to the disease as a result of frequent subclinical / clinical infection.

Laboratory investigations are not always helpful in establishing or disproving a diagnosis of enteric fever. The most important diagnostic test is the isolation of the causative organism from the blood. Isolation attempts are often unsuccessful late in the illness and in partially treated cases. But the widal reaction is useful only when it is possible to demonstrate a four fold rise or more in the antibody titre during the illness. This is possible only when the first sample is available from the early stage of illness. The interpretation of the results of widal test will also have to be based on considerations of antibody level of healthy population, age group, history of TAB Vaccination and many other factors. So in this circumstances, isolation of the organism from blood, urine or motion is very important.

The introduction of chloramphenicol in the treatment of typhoid fever was a remarkable milestone[10]. But the development of resistance to chloramphenicol was a

major hazard in the past with the outbreak of two epidemics one in Mexico and another in Calicut in 1972. Both were chloramphenicol resistant. This has brought drugs like cotrimoxazole, furazolidone, Ampicillin, Amoxycillin in the treatment of typhoid fever. As there is a variety of drugs at the disposal of the clinician in the treatment of typhoid fever, it has become necessary to ascertain the relative merits and demerits of the individual drugs. Presently 3rd generation cephalosporins and quinolones especially ofloxacin constitute the first line therapy.

Until 1950, these antibiotics were effective in patients with acute infection reducing complications and mortality. However since 1950, progressive resistance to one or more of these first line antibiotics has been reported in 1989. Resistance to all three first line antibiotics was noted in Pakistan, India, China and Arabian Gulf. There is increasing incidence of multidrug resistant typhoid fever (MDRTF) which needs close monitoring[11,12].

Immunization against typhoid fever was developed as early as 1896 using a whole cell vaccine consisting of heat killed Salmonella typhi preserved in phenol. But this vaccine had very high incidence of side effects and was not universally acceptable. There are newer vaccines both injectable typhi Vi and oral Ty 21a vaccine which are potent as well as quite safe to administer. Vi polysaccharide conjugate vaccines, (Linked to the diphtheria and the tetanus toxoid proteins), mutant strains 541 Ty and 543 Ty by genetic engineering techniques are in progress.

AIMS OF THE STUDY

1. To Study the age incidence, symptoms and signs profile in patients with typhoid fever.

2. To study the incidence of complications in patients with typhoid fever.

3. To study the culture and antibiotic sensitivity profile in typhoid fever patients.

REVIEW OF LITERATURE

HISTORY[1]

Until 1st Quarter of 19th Century typhoid fever was not recognised as a distinct clinical entity and was confused with other prolonged febrile syndromes particularly typhus fever of rickettesial origin.

Typhos in Greek means smoke. Typhoid (Typhus like) got its name because it was so like typhus. Twisting the Greek word a little, we get phytos that meant rottenness or putrescence, the putrid malignant fever that was typhoid different from slow nervous fever that was typhus, described by Huxham in 1782, the typhoid fever was known as phytogenic fever owing its origin to such substances.

Historical Overview of typhoid fever

Year	Discovery
1782	Huxham described two fevers The slow nervous fever – Typhus Putrid malignant fever – Typhoid
1829	Dr. P. Louis in Paris described typhoid clearly separating it from other fevers
1837	Gerhardt in Philadelphia (USA) pointed out that it was impossible to confuse the intestinal lesions of typhoid with pathological findings in typhus.
1850	William Tenner's book "On the identity or Non-identity of typhoid typhus fever" settled the issue of identity of typhoid fever.

1869 The term Enteric fever was introduced.

1873 William Budd an Englishman wrote epidemiological masterpiece providing evidence that bowel discharges were the main sources of infection that the disease was waterborne and milk, food, contaminated linen and other fomites were sources of dissemination and insisted without proof that a specific germ caused typhoid fever. During the Spanish American war, Typhoid fever was the most common course of military casualty. An army commission studied the problem and their evidence established the epidemiological importance of faeces from cases of typhoid fever.

1880 Typhoid bacillus was first observed by Eberth in the mesenteric nodes and spleen of fatal cases of typhoid fever.

1884 The bacillus was first cultivated and isolated in pure culture from spleen of infected patients. It came to be known as the Eberth Gaffky bacillus or Eberthella typhi

1885 Salmon and Smith described a bacillus causing Hog Cholera. This is now called as Salmonella cholera suis. It was the first of a series of similar organisms of the genus salmonella. It was subsequently realised that the typhoid bacillus also belonged to this group. It was named in honour of Smith's supervisor Dr. Daniel Salmon. The genus Eberthella had been abolished. Other workers followed by isolating the organism from skull, urine, rose spots and gall bladder.

The Choice of the designation salmonella enterica reflects a desire to avoid confusion with the prototypic organism described by Smith. Most human pathogenic salmonella fall within subspecies enterica. Thus *S. typhi* should be called S. enterica subspecies enterica serovar typhi.

1896 Pfeiffer and Kolle made the first vaccine for human use from heat killed organism.

1896 Durham and Widal each independently reported that convalescent phase serum mixed with *S. typhi* caused the organism to stick together in large balls and lose their motility. Thus was born the term agglutinins and classical serological test, Widal test.

1897 Wright and Semple introduced a vaccine consisting of suspension of typhoid killed by heat and injected subcutaneously. It was used with success in India before the great war and had a great success during the 1914-1918 war.

1903 Robert koch outlined three logical methods of typhoid control. Disinfect the excreta and its source, improve sewage handling and isolate convalescent patient until they become bacillus free.

1909 Wasreh Coleman established the usefulness of high protein diet to minimize the debilitation in typhoid fever.

1948 Theodore woodward showed that chloramphenicol sterilized the blood cultures of typhoid fever patients thus ushering the modern era of antibiotics for treatment of typhoid fever.

MAGNITUDE OF PROBLEM

Typhoid fever occurs all over the world. Known global hotspots for typhoid fever include Peru, Alexandria, (Egypt), Jakarta (Indonesia), India, Pakistan and Nepal[12]. The incidence, mode of transmission and consequences of typhoid fever

differ significantly in developed and developing countries. The incidence has decreased markedly in the developed countries.

The developing countries reporting high number of typhoid fever cases share several characteristics like rapidly increasing population, rapidly increasing urbanisation, inadequate facilities for processing human wastes, decreasing water supply per capita, intimate contact between humans, heavily contaminated water supplies and over burdened health care delivery system.

Typhoid fever is a major public health problem in India. The Disease is endemic in almost all parts of the country with periodic outbreaks of water borne,food borne diseases. In India most of the cases of typhoid fever occur in 5-39 year age groups. Multiple Drug Resistant Typhoid Fever (MDRTF) is now posing a big problem. Over 70% of the clinical isolates of *S.typhi* in our country have shown Multiple Drug Resistance[13,14,15].

Typhoid fever is not an uniformly notifiable disease throughout the country. The estimated number of annual cases in India alone should be around 4.5 million of which only 0.3 million cases are reported.

Epidemiology

The epidemiology of typhoid fever makes fascinating reading. The incubation period ranges between 1-3 weeks, average being 2 weeks. It is inversely related to the

inoculation size. The normal flora of the intestine may be an important defense against invasion by typhoid bacilli. The major sources of outbreaks are food and water. Typhoid fever has a low risk of contagious spread. During 1989-96, several MDRTF outbreaks have been reported from different parts of India. The fact that almost 90% of the resistant isolates belonged to a single phage type E suggests that there could have been a common source of infection.

The incidence of disease increases during the summer, though the cases continue to occur throughout the year. The peak is usually during July – September. The typhoid fever may occur at any age. But it is a disease of children (aged 8-13 years) and young adults. Older citizens appear to be relatively immune, because of frequently reinforced acquired immunity i.e., numerous subclinical exposures to typhoid bacilli. But there is no subclinical exposure in holiday typhoid and people of all age groups are equally susceptible.

There is no data to support racial and gender susceptibility. The females have a special predilection to become chronic carriers though there is male preponderance because of the greater mobility. Laboratory personnel are at high risk of acquiring infection. Cooks who are carriers pose a great threat of causing outbreaks.

Early in this century, a middle aged Irishwoman named Mary Mallon migrated to New York Sate to work as a cook in the houses of rich. What followed has gone into the history as the classic example of a chronic carrier state. Seven of the eight

families for which Mary worked over a seven-year period were stricken by typhoid fever and several persons died.

Socio Economic factors

The association of poverty with inadequate sanitary facilities and questionable water supplies enhances the opportunity for this segment of the world's population to acquire every type of enteric infection especially typhoid fever type. Malnutrition enhances the susceptibility to typhoid infection by alterations in the intestinal flora or other host defenses.

Reservoir of infection: Human beings are the only known reservoir and natural hosts of *S. typhi*. The bacilli are spread by carriers and cases. The cases may be clinical or subclinical. *S. typhi* has on occasion been detected from the blood of even healthy persons.

Communicability lasts as long as the salmonella are present in the stool or urine. The chronic carrier state may last even up to 50 years, more commonly in women who often have gall stones[16]. Faecal carriers are more frequent than urinary carriers. Chronic urinary carriers state is often associated with some abnormality of the urinary tract.

Routes of Transmission[16,17]

1. *S.typhi* gain access to the body through oral route in almost all cases as a consequence of contamination of food, water and milk.

2. The role of water in the spread of typhoid fever is well known. In sewage irrigated soil *S.typhi* may survive for upto 2 months. Sea water is bactericidal. *S. typhi* can survive for more than a month in ice or ice cream. Patients with parasite infection such as roundworm or schistosomes are readily infected with *S.typhi*. Schistosomiasis causes tissue scarring and *S.typhi* can remain indefinitely in the scar tissue.

In Salmonella typhi endemic regions the rate of clinical typhoid among person positive for HIV is approximately 25 fold higher than that among HIV negative individual.

Water borne infection[17]

Waterborne infection is explosive because of the simultaneous drinking of water by a large number of people. There is tendency for the period of waterborne typhoid fever to be longer than the usual 10-14 days because the affecting dose is small. It will often be the case that the contamination of the water has ceased long before the occurrence of cases of typhoid fever that lead to bacteriological examination of water.

Typhoid fever is caused by Salmonella typhi. Paratyphoid fever is caused by S. paratyphi A, B and C. The term typhoid fever combines both typhoid and paratyphoid fever. However because typhoid is fundamentally not an enteric disease the term “Enteric Fever” is also inappropriate.

Typhoid fever is still the best term for all clinicians to describe a particular syndrome i.e., in fact due primarily to Salmonella typhi and Salmonella paratyphi A,B,C. Clinical typhoid fever is almost always due to human adapted salmonella.

Salmonella typhi are gram negative bacilli which are non acid fast, non-capsulated and non sporing. They measure approximately 4 micron x 0.6 micron. The organism is motile with the help of peritrichous flagella. Type I Fimbriae are present on the surface of Salmonella typhi.

As the majority of serovars have been named after the place in which they are first detected for example Heidelberg or Newport, salmonella nomenclature seems more geographic than microbiologic. Another commonly used historic classification for Salmonella isolates is on the basis of the major representatives of Phase – I somatic antigens that they express.

Biological Characters[17]

Survival in H_2O

S.typhi survive longer in aerobic than in anaerobic and also in organic matter than clean water. Water gets contaminated by faeces or urine of infected patients, carriers.

Any defect in storage of water may permit presence of organic matter and longer survival of *S.typhi* which may lead to outbreak of typhoid fever.

Infection from travel

The danger of acquiring typhoid fever remains a travel hazard for developed countries from developing countries, since there is less likelihood of any subclinical exposures to Salmonella.

Cross infection and Secondary cases

Nurses, Laboratory staff are at risk if they render careless handling of the specimens. In mental hospitals cross infections are much common, for it is difficult to maintain rigid standards of personal hygiene. There are reports of typhoid fever by cross infection from endoscopes and polyvinyl duodenal tubes.

In sanitary surroundings in backward countries flies may be an important source of infection[18].

S. typhi belongs to the family Enterobacteriaceae as species S.enterica sub species enterica serovar typhi (Sero group D)

Cultural Characteristics[17]

Typhoid bacilli grow rapidly on ordinary media over a range of pH6-8 and temperature range of 15°C-41°C. Optimum being 37°C. Various media have been used for the enrichment of Salmonella. The ability to grow in the presence of bile has been made use of in making the selective media.

Macconkey and desoxycholate citrate media colonies are colourless due to absence of lactose fermentation. On Wilson and Blair Bismuth Sulphite medium, Jet black Colonies with a metallic sheen are formed due to production of H_2S.

Selenite F and tetrathionate broths are commonly employed as enrichment media. Iron starvation has shown to limit the growth of *S.typhi* in culture.

Biochemical Reactions

Unlike other Salmonella, *S.typhi* does not produce gas from fermentation of carbohydrates. *S.typhi* does not ferment lactose, a property which is used for initial selection of the organism in the clinical and microbiological laboratory.

IMMUNOLOGY

Antigenic Structure of Salmonella[17]

The Salmonella carry a complex antigenic structure. The antigens which have been detected include.

Flagellar (H) Antigen

Somatic (O) Antigen

Surface (Vi) Antigen

Fimbrial (F) Antigen

M and N Antigen

R antigen present on the rough strains

‘H’ Antigen – composed of fibrous proteins called flagellins. It is heat stable and alcohol labile, but is well preserved in 0.2% formaldehyde. When mixed with antisera H suspensions, it agglutinates rapidly producing large loose fluffy clumps.

The H antigen is strongly immunogenic and induces antibody formation rapidly and in high titre following infection or immunisation. The flagellar antigen is of dual nature occurring in one of two phases. Phase I containing more specific and Phase II containing less specific antigen.

O Antigen

The somtic O Antigen is a phospholipid protein polysaccharide complex, which forms an integral part of the cell wall. It is identical with endotoxin. It can be extracted from the bacterial cells by treatment with trichloroacetic acid, as first shown by Boivin and therefore called the Boivin Antigen.

When mixed with antisera, O Suspensions form compact, chalky, granular clumps. The O Antigen is less immunogenic than H and the titre of O antibody induced after infection or immunisation is generally lower than that of the H antibody. The O Antigen is not a single factor but a mosaic of two or more antigenic factors. ‘O’ and ‘H’ antigens are used in the characterisation of the organisms and antibodies to them are used in the serodiagnosis of typhoid fever and widal test.

Vi Antigen

The Vi (Virulence) antigen is a surface polysaccharide which is formed by most strains of *S.typhi* and some strains of S. paratyphi C, S. dublin and Citrobacter freundii. The Vi antigen is heat labile and is destroyed at 100°C within 60 minutes. Antibodies to Vi antigen are shown to be protective against typhoid fever.

S. typhi falls in the group of salmonella according to the classification by Kauffmann and White. Its antigenic formula established on the basis 'O' and 'H' antigens is 09, 12 (vi), d. *S. typhi* exhibits a remarkable degree of homogeneity as compared to other salmonella and rarely exhibits biochemical or serological variability.

Intracellular habitat

Typhoid bacilli are able to achieve an intracellular habitat promptly after oral ingestion. This property may account for the prolonged duration of the disease in untreated patients and the slow response to antibiotic therapy. Inside the cell, the organism appears to be protected from the hosts attempts to eliminate it through specific immune mechanism, circulating antibiotics or constrained intra cellular cytolytic processes.

Virulence Factor[17]

S. typhi is an invasive intracellular bacterial pathogen that maintains several virulence factors which enable it to enter and survive with its human host.

The virulence factors of *S. typhi* are due to:

1. Lipopolysaccharride
2. Motility
3. Adhesins such as Fimbriae
4. Iron Siderophores
5. Polysaccharide capsule (Vi antigen)

Knowledge of virulence factors at the molecular genetic level will lead to development of better and effectives vaccine to combat this important disease.

Other Factors

Vi (Virulence) Factor

Vi containing strains are more virulent. Vi antigen interferes the phagocytosis by preventing the binding of C3 to the surface of bacterium. The sequence of gene (Vi B) encoding Vi antigen has been defined. Vi Antigen increases resistance to the Cytolytic effect of hydrogen peroxide allowing typhoid bacilli to persist in resting macrophages.

The ability of organisms to survive within macrophages after phagocytosis is an important virulence trait encoded by the phop regulan.

PATHOGENESIS OF TYPHOID FEVER

The pathogenesis of Typhoid fever has been studied using *S. typhi* in naturally infected humans and in volunteers. The pathogenesis of salmonella typhoid fever has been studied using *S. typhi murium* and S. enterititidis in the murine typhoid model and for *S. typhi* in naturally infected humans and in volunteers.

Human beings are the only known hosts at present that are susceptible to *S. typhi*. The gastro intestinal tract's non specific defense mechanism of the host is an important barrier against this disease. Infection is initiated by oral ingestion of organisms, which must pass through the gastric acid barrier to establish infection. While experiments with volunteers have suggested that 10^5 organisms are required for the initiation of infection, buffering of acid by food lowers the necessary inoculum in natural exposures, and the actual infectious dose is probably considerably less than 10^5. No significant association between dose and severity of illness exists, although both a direct relation between dose and attack rate and an indirect relation between dose and incubation period exist. Severity is determined by both host and microbial properties as discussed below.

Salmonella exhibits a genetic adaptive acid – tolerance response, exposure to acid leads to synthesis of at least 40 proteins, some of which may play a role in pathogenesis. Bacteria successfully evading "acid death" in the stomach pass on to the distal ileum and colon, where they penetrate the mucosal barrier. Most new

information about Salmonella pathogenesis has been derived from a combination of studies.

Genetic factors related to the Pathogenesis

1. Entry of the organism into the epithelial cells is controlled by a number of genes clustered on the salmonella chromosome. The protein products of these genes are essential to the synthesis of certain as yet unidentified proteins that induce endocytosis of salmonella.
2. Genes contributing to the virulence of the organisms e.g. Pho P and Pho Q are related to the resistance of the organism to gastric acid and cationic antimicrobial peptides. The pho P and pho Q system promotes survival of the organism within macrophages. Another system called the crp-cya system has been found to be important for typhoid fever pathogenesis.
3. The major surface carbohydrate containing molecules of salmonella especially the lipid A component of the LPS is an essential virulence determinant that could lead to the development of septic shock.

Host Defenses

Various host defenses are important in resisting intestinal colonisation and invasion by Salmonella.

Gastric Factors

Normal gastric acidity < 3.5 pH is lethal for salmonella.

Intestinal Factors

Normal intestinal motility sweeps the salmonella quickly. Normal intestinal flora liberate short chain fatty acids, which are toxic to salmonella. Alteration of intestinal anaerobes by antibiotics render the host more susceptible. Secretory or mucosal antibodies also are thought to protect against salmonella. Animal strains generally resistant to intestinal invasion have been described.

Non-Specific and other possible factors

Nutritional state, lactoferrin, Lysozyme are also determining the host defence.

Factors increasing susceptibility to Salmonellosis

Achlorhydria and gastric surgery, haemolytic anaemias especially sickle cell anaemia and other Haemoglobinopathies, Carcinomatoses, Leukemias, Lymphomas and immuno suppressive drugs leads to salmonella invasion easily. Inoculum's size and type of vehicle in which it is ingested, greatly influence the attack rate as well as the incubation period of the disease.

Typhoid fever is a protracted disease that includes bacteremia with fever and chills during the first week, widespread reticuloendothelial involvement with rash, abdominal pain and prostration in the second week; ulceration of peyer's patches with intestinal bleedings and shock during the third week.

The symptoms and signs of typhoid fever may not be due to circulating endotoxins. Most patients of typhoid fever have no detectable serum endotoxins. However in patients with septic shock syndrome circulating endotoxin can be demonstrated in which there is a high mortality rate and require combination therapy of steroids and antibiotics.

The pathogenesis of carrier state has never been clearly defined. It is apparent that the gall stones or a malfunctioning gall bladder predisposes to carrier state and *S.typhi* can remain inside stone and not be affected by antibiotics.

PATHOLOGY

The pathological lesions in cases of typhoid fever are observed in intestines as well as in other organs.

Intestinal Lesions

The terminal ileum is most often affected, though the lesions may be seen in jejunum or colon. The lymphoid patches initially show an inflammatory swelling followed by about the 10^{th} day, necrosis and ulceration. The peyer's patches show typhoid ulcers with their long axis along the length of the bowel corresponding in shape and extent to the lymphoid paths. Healing of these lesion leaves with smooth silky scar that never shows stricture formation.

Severe haemorrhage sometimes from necrotic ulceration, extensive necrosis along the length of the small bowel, rupture of lymphnodes usually leads to fatal peritonitis. Microscopically the inflammatory changes are due to Typhoid histiocytes and the development of necrosis may well represent a delayed hypersensitivity reaction.

Extra intestinal lesion

The spleen is markedly enlarged due to proliferation of mononuclear phagocytes in red pulp. Liver shows focal aggregates of typhoid nodules from kupffer cells. These typhoid nodules also occur in the bone marrow and lymphnodes. Gall bladder shows cholecystitis which might account for the carriers. Muscles of abdomen shows zenker's degeneration (focal necrosis). Typhoid endotoxaemia leads to laryngitis, bronchitis and Pneumonia. Other lesions include endocarditis, meningitis, arthritis, orchitis, periostitis and osteomyelitis. The effect of *S. typhi* can be manifested in multiple organs as abscesses, granulomtaous inflammation and lymphoid hyperplasia.

IMMUNITY[19]

The *S. typhi* infection is a particularly difficult challenge for host defense mechanisms due to the multifaceted nature of the infectious process. The recovery from infection is generally accompanied by the development of significant level of immunity, however the disease does not confer complete immunity. Relapse may

occur in up to 15-20% of typhoid patients who have recovered from first infection and up to 5% may even fail to develop any detectable immune response.

There are many mechanisms of protective immunity induction in typhoid fever. Immunity to salmonella infection produces antibody to all 3 antigens. Because of the complex nature of the pathogenesis of *S. typhi* clinical infection, a protective role is probably played by all the following:

- The secretory intestinal antibody (Ig A) in preventing mucosal invasion
- The circulating antibody against bacteraemia.
- The cell-mediated immunity in eliminating intracellular bacilli.

Immune response after vaccination

The circulating and cell mediated secretory immune response is stronger after natural infection than after vaccination and both includes prominent serum and CMI (cell mediated immunity) components.

Table 1

Types of immune response elicited by various vaccines and diseases

Vaccine	*Serum Antibodies*	*Intestinal Secretory antibodies*	*CMI**
Parenteral Intra Cellular	+++	+	0
Live Oral Ty21A	+/++	++/++	++
Vi Polysaccharide	+++	?	?
T.F.	++++	++++	++++

** Antibody dependent cellular cytotoxicity CMI response*

The immune response depends upon the nature of the vaccine.

Parenteral killed whole cell vaccines elicit a serum response equal to a natural infection but not a comparable CMI. Live oral vaccines elicit a good CMI and a good antibody response. Hence the 3 groups of currently available antityphoid fever vaccines act through 3 different mechanisms signifying the role played by different components of the immune system in protection. Ty21a is able to induce long-term immunological memory.

To sum up, it has been seen that several humoral and cell mediated immune responses have been shown to be highly protective. The relative contribution of serum antibodies versus CMI in protection against diseases is unknown. However, given the fact that *S.typhi* can survive intracellularly, the cellular arm may be more important. While inactivated vaccines may tackle the systemic phase of the disease, live or oral attenuated vaccines appear to interfere with the infectious process by means of a local mucosal immune response.

CLINICAL FEATURES

Typhoid fever is predominantly an infection of children and young adults, the average incubation period is 7-21 days while the extremes of range being 3-60 days. Mild and unapparent infections are common especially in endemic areas. Despite the huge diversity of clinical features there are often few specific findings to assist clinical diagnosis in the early stages. The clinical manifestations of the illness vary markedly from patient to patient. Mild form of the disease may last only a week and

in untreated cases it may be prolonged up to 8 weeks or more. In a typical case if not treated with antimicrobials the illness lasts for about 4 weeks.

The onset is insidious, may be abrupt in children, with headache, body ache, lassitude and abdominal discomfort, coated tongue and fever. Headache is a common manifestation of the disease and is usually severe. Fever almost always accompanies these indefinite symptoms of illness. The fever is in step ladder pattern. Initially, a gradual rise in step-wise fashion occurs with daily increments of 1-2°F until after 5-7 days a sustained temperature of 102-106°F is present.

Without appropriate antimicrobial therapy, the temperature remains at this level for approximately 10-14 days. With convalescence, fever diminishes, also in step wise fashion over several days. Shivering attacks may occur. Abdominal discomfort, bloating, constipation are common symptoms in the early phase. There is usually diarrhoea (Pea soup stools). Tongue is coated in children in the centre with reddish margins (Typhoid V tongue). A bronchitic cough is common in the early stages of illness. Epistaxis as a prodromal symptom may be present in few cases. Mental dullness and delirium may occur.

Physical examination in the first week reveals relative bradycardia in minority of patients. Tachycardia is usual feature in children. Relative bradycardia may carry greatest diagnostic significance for typhoid in febrile children. During 2nd week rose spots appear in crops as small, pale red blanching slightly raised macules, not

exceeding 15-20 number in the periumbilical region and lower chest are reported in western countries. It varies in white and black races and is difficult to see in dark individuals. Certain studies especially from Asian and African countries report the incidence of rose spots only in 10% cases. Typhoid bacilli can be cultured from these spots.

Abdomen is moderately distended with vague tenderness especially over right iliac fossa. Palpation may reveal gurgling secondary to mild distension of ileal loops. Over 75% cases show moderate splenomegaly which is soft and at times tender. Liver may also be enlarged in a few cases. During 3rd week mild cases show gradual fall of temperature when toxaemia abates. In severe and untreated cases toxaemia leads to complications in the form of intestinal haemorrhages or perforation or peritonitis. One of the most striking features of typhoid fever into the third week of illness is the facial appearance which is distinctive enough to merit the term ***"typhoid facies"***.

In a typical uncomplicated case, fever subsides in about 4 weeks, appetite returns, tongue clears, and hydration improves and weight increases. The major characteristics of untreated typhoid are persistent high fever, severe anorexia, weight loss and changes in sensorium.

Complications develop in the 3rd week in untreated cases in the form of gastro intestinal haemorrhage, perforation, appendicular abscesses, pyelonephritis, meningitis, peripheral circulatory failure, apart from what is already described as the

normal course of events in uncomplicated typhoid fever. Various other clinical presentations are described in literature. This is especially important in areas where typhoid fever is endemic and use of broad spectrum antibiotics is in vogue for all febrile illnesses. This diagnosis in these cases may also be due to the fact that the widal response may be deceptive.

The unusual clinical manifestation described in typhoid fever are:

Gastrointestinal

- Meteorism
- Intestinal Haemorrhage
- Intestinal Perforation
- Acute Cholecystitis
- Acute Pancreatitis
- Non Perforating peritonitis
- Hepatic abscess
- Appendicitis
- Splenic abscess
- Parotitis
- Jaundice
- Pneumoperitonitis

Respiratory

Bronchitis

Acute lobar pneumonia

Laryngeal ulceration

Pneumothorax and Pleural effusion

Cardiovascular

Myocarditis[20]

Phlebitis and arteritis

Pericarditis and endocarditis

Asymptomatic ECG changes

Deep vein Thrombosis

Shock and sudden death

Genito Urinary

Retention of Urine

Glomerulonephritis

Pyelonephritis

Cystitis

Typhoid nephritis

Haemopoietic

Haemolytic anaemia

DIC

Haeomolytic Uraemic Syndrome

Bones, Joints and Muscles

Periostitis

Typhoid spine

Rupture of muscles

Skin and Hair

Furunculosis

Bed Sores

Alopecia

Thin, brittle nails

Neuropsychiatric

Delirium

Psychotic state

Depression

Deafness

Meningitis[21]

Acute Disseminated Encephalomyelitis

Transverse myelitis

Upper motor neuron lesions

Extrapyramidal disorder

Optic neuritis

Peripheral and Cranial Neuropathy

Guillain Barre Syndrome

Pseudotumour cerebri

Raised intracranial tension

Cerebrothrombosis

Acute cerebellar ataxia

Chorea

Aphasia

(No permanent residual sequelae)

Relapse

Others

Hypercalcaemia

Decubitus ulcerations

Abortion

Post – typhoid anhidrosis[22]

A long list of complications of typhoid fever can be drawn up very easily with symptoms and signs referred to most systems of the body. Indeed it used to be said

that to know typhoid fever was to know the whole of clinical medicine, if the student has not already covered the field by studying the complications of syphilis.

Typhoid fever in patients with HIV

Patients who are positive for HIV are at significantly increased risk for infection with *S. typhi* and S. paratyphi

- ❖ Increased frequency of acute gastroenteritis
- ❖ Prolonged bacteremia and severe disease
- ❖ Recurrence / relapse is more common
- ❖ Requires more than one antibiotic for much longer time for treatment
- ❖ Chances of development of drug resistance are more
- ❖ Breakthrough bacteremia despite antibiotic therapy.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes infections associated with prolonged fever such as miliary tuberculosis, malaria, viral hepatitis, leptospirosis, rickettesial infections, brucellosis, tularaemia, CMV infections, as well as non-infectious causes such as lymphoma.

The presentation of typhoid fever may vary widely. In areas which are endemic for a large number of communicable diseases it is extremely necessary to differentially diagnose typhoid fever from other common ailments.

Fever is primary manifestation of a large number of important infectious diseases including typhoid fever. The following conditions should always be kept in the differential diagnosis of typhoid fever.

Malaria

Rigors are not common in typhoid fever though they may occur. Malaria and typhoid fever can occur together in the same patient. Sudden onset, wide diurnal variations in body temperature, early splenic enlargement, malarial parasites in blood and response to antimalarial drugs are distinguishing points in favour of malaria.

Viral Hepatitis

It may mimic typhoid fever in the pre-icteric stage. But marked nausea and vomiting, hepatic tenderness and high coloured urine are some of the distinguishing features in favour of viral hepatitis.

Amoebic Hepatitis / Abscess

Pain in right hypochondrium and lower chest, moderate fever, enlarged tender liver, right hemidiaphragm elevation and being immobile on fluoroscopy are points favouring amoebic aetiology.

Typhus Fever

Clinical picture is characterised by an acute infectious process lasting 1-3 weeks. Symptoms are high fever, prostration, mental aberrations and a rash developing towards the end of first week. The rash is more profuse and deeper in colour.

Rheumatic Fever

In typhoid fever the joint pains may be more severe at times and the temperature swings being more than usual, the illness may resemble quite closely the early stages of rheumatic fever, but the rheumatic patient is more likely to be alert and apprehensive and the typhoid patient more toxic and troubled.

Meningitis

Though typhoid fever is typically a septicaemic, febrile illness symptoms referable to one system may sometimes dominate the early clinical picture. Headache may be so severe as to simulate meningitis, though at times *S. typhi* can cause meningitis also.

Subacute Bacterial Endocarditis (SABE)

The points in favour of SABE include

- Fever seldom continuous or high
- Frequent chills with septic type of temperature
- Cardiac signs

- Anaemia
- Embolic phenomenon,
- Positive blood culture for low virulence organisms such as coagulase negative staphylococci and Streptococcus viridans.

Kala-Azar

Kala-Azar may have typhoid fever type of onset. There is progressive splenic enlargement. Characteristic double rise of temperature occurs with good appetite and without features of toxaemia.

Brucellosis

An epidemic disease of long duration characterised by fever, continuous, remittent or intermittent in type, in most cases enlarged spleen, profuse perspiration, listlessness accompanied by pains of a rheumatic or neuralgic character, arthralgia or swelling of joints. Agglutination test for brucellosis is positive.

Tularaemia

"Typhoid type" may occur in laboratory workers. Sudden onset with headache and fleeting pains, pyrexia may subside to normal or nearly so on 3rd day to 6th day. Spleen is not palpable.

Pyelitis or Septicaemia

It is usually due to Escherichia coli organism. In this there is high fever, though not of continuous type, may last for 2-3 weeks. Tenderness in loins, pus in urine, leucocytosis or positive blood culture for *E.coli* are the findings.

Infectious Mononucleosis

Abrupt onset with sore throat, prolonged pyrexia, the temperature at first is remittent and may later become intermittent. Considerable constitutional disturbance, papular or maculopapular rash chiefly on trunk. Spleen is rarely enlarged. Late glandular enlargement is seen.

Collagen Vascular diseases (SLE or PAN)

Symptoms and signs referable to multiple organ systems. Weakness and weight loss.

Miliary Tuberculosis

Increased respiration, irregular temperature, tachycardia, cough and cyanosis. Symptoms referable to alimentary tract are less pronounced.

Abscess

Abscess anywhere, Subphrenic, Pelvic, Renal, Muscular or even dental may give rise to continuous fever with little, if any, localising signs and repeated blood cultures may fail to give any clue.

Appendicitis

Abdominal pain is occasionally severe and it is sometimes quite difficult to differentiate typhoid fever from appendicitis, a while cell count may be of value.

TB Peritonitis

Slow onset, continuous fever and caseous masses palpable.

Influenza and unspecified viral fevers

When at times no diagnostic clues are forthcoming and the febrile patient with his headache, malaise and myalgia is labeled to be suffering from “influenza” or viral fever whereas the actual diagnosis may be typhoid fever.

LABORATORY DIAGNOSIS

Laboratory diagnosis of the typhoid fever depends upon three important components which are:

- Isolation of the organism
- Detection of microbial antigen
- Titration of antibody against causative agent

Blood (or bone marrow or clot), stool and urine are the possible clinical samples from which the causative agent can be isolated in typhoid fever cases. However the isolation rate is different at different stages.

A. CULTURE

Blood Culture

S. typhi may be cultured from venous blood in 90% of cases during the first week or 10 days of the illness. By the 3rd week, chances of obtaining a positive blood culture roughly halves. The sensitivity is 80-90% in the 1st week and reduces to 50% by the 3rd week. In patients dying from toxaemia, the organism persists in the bloodstream till the end. Blood should be diluted 4 times but in patients treated with antibiotics, blood should be diluted 10 times.

Clot Culture

The bactericidal property of blood seems to be concentrated mainly in the serum, so that when it is removed for serological testing the clot should be cultured. It is not uncommon for clot culture to be positive when blood culture is negative. The sensitivity is 69-84%

Bone Marrow Culture

It is often positive when blood cultures are negative because the organism can lurk thereafter it has left the blood stream, especially more so, in patients treated with antibiotics. Bone marrow culture is indicated in prolonged febrile illness of unknown origin and secondly in patients with severe prolonged neutropenia.

Faecal Culture

Faecal culture is positive in the 1st week in 56% cases. The positivity increases in the 3rd week to 75%. However, a negative report does not rule out the diagnosis of typhoid. Faecal culture is taken from a properly sterilised bedpan in a special container. Rectal swabs are not useful in diagnosis.

Urine Culture

Urine Culture is positive in a quarter to one third of cases, but there seems to be no regular excretion pattern as in faeces.

Bile Culture

This may give positive results more often than blood, bone marrow or urine. A convenient method is by using a string capsule or by duodenal intubation. Duodenal and jejunal tubes can be inserted during the procedure of endoscopy. Pure culture, free from intestinal organisms can be obtained. In determination of carrier, bile culture is most reliable.

Culture of rose spots

Skin snips from rose spots can be cultured. It is useful in patients who have taken antibiotics, because antibiotics sterilize the blood stream, but leave the organisms alive in the rose spots and bone marrow.

B. SEROLOGIC TESTS

The Widal Test[23,24]

In an uninoculated patient living in non endemic area, the result of a single test with a titre of 1:40 in the 1st week of a febrile illness may be given some significance. If the titres are 1:80, the diagnosis is almost certain. A four-fold rise in paired sera over a week should be given more weightage. However, there are several factors that obscure the serological picture and reduce the value of Widal test.

1. False positive result is seen in patients previously exposed to other salmonella, Shigella and Coliforms. The antigens that stimulate antibodies (O, H, and Vi) are shared by a large number of salmonella and related group of organisms, including Coliforms. A positive agglutination reaction may therefore, merely indicates contact with any organism, dead or alive, recently or in more distant past, Salmonella or other, that posses any one of the relevant antigens.

2. The production of antibodies may be stimulated by the antigens of dead organisms as in TAB vaccination. Antigens of *S.typhi*, paratyphi A and B are present in the vaccine and so antibodies to all 3 will be present in patient's serum. But O antibodies tend to disappear rather quickly so that after 6 months to a year, the titre is likely to be quite low. *S.typhi* O Titre more than 1:640 in an unimmunised patient may be given some significance in a febrile patient, but it is not specific.

3. False positive result is seen in those with chronic liver disease, having high serum globulin levels and in several major immunological disorders.

4. The Widal test contributes nothing of diagnostic value, when the organism has been cultured. Positive Widal test was seen only in 74% of a large series of African children with Typhoid proved by blood culture.

5. The typical 4 fold rise in Widal titre in the 2nd week of fever is no more classical. In one study of 100 cases of typhoid fever in Kuala Lumpur 2/3rd patients showed no such rise in titre.

6. Treatment with antibiotics alters the response. But treated or untreated, the measurement of H and O antibodies in a patient's serum, seems to relate very poorly to the clinical or immunological state of the patient.

7. Anamnestic reaction. Once Typhoid antibodies have been produced in a patient, it can be stimulated again, when exposed to any other infection or antigenic challenge. This means that Widal test can be positive in any other febrile illness, in a patient already exposed to typhoid organisms in the past.

In the face of all the complicating factors discussed above, the Widal test thus has very little diagnostic significance.

The test may carry some significance in persons coming from nonendemic area, who are not inoculated. Similarly a conspicuous serial rise in antibody titre, in culture negative cases of Typhoid, may be given significance.

Other Serological Tests

1. Latex agglutination test for rapid diagnosis of Typhoid fever is found to be useful and sensitive in patients with prior history of antibiotic therapy. Sensitivity is 78%. It is useful in diagnosis of culture negative cases.

2. Staphylococcal Slide Coagglutination test (SSCoAg)

   It is positive in 86.6% cases where Widal is negative. It is almost always positive in culture positive cases. It is negative in 5% cases of Typhoid, indicating that a negative test does not exclude typhoid fever.

3. Counter immunoelectrophoresis (CIE)- It is done using Veronal buffer extract and lipopolysaccharide of *S. typhi*. It seemed more reliable and specific for serological diagnosis of Typhoid fever than Widal. However, they have the same disadvantages as Widal.

4. ELISA - It has been used to detect Vi antigen in the urine of patients. Similar tests have been used to detect monoclonal antibodies in blood. Vi antibodies typically rise after 3-4 weeks of illness and are of less value in the early diagnosis of the illness.

Rapid detection of antibodies (Modification of Widal test)

- Use of coloured antigens
- Rapid slide test
- Estimation of IgM Vi IgG antibody.

Though not available widely for routine diagnosis of typhoid fever, DNA probes, use of monoclonal antibodies and PCR are being tried for the rapid and specific diagnosis.

C. OTHER INVESTIGATIONS IN TYPHOID FEVER

The haemoglobin tends to be low. Post haemorrhage polychromasia and reticulocytosis is seen. Haemolytic anaemia is seen in patients with G 6 PD deficiency. Leukopenia occurs in some patients. Coinfection with Malaria should be ruled out[25].

Liver enzymes may get elevated; SGOT values of 40 to 185 IU and SGPT values of 50-160 IU are seen. Rise of bilirubin in the range of 2.2 to 12 mg% is seen.

DIC profile including PT, PTT and FDP levels tend to be elevated secondary to typhoid hepatitis and / or Septicaemia.

X-ray chest may reveal features of Typhoid pneumonia or ARDS. Urine picture may show hematuria and proteinuria with casts in patients with nephrotyphoid.

An abdominal ultrasound is essential for the diagnosis of silent perforation or pelvic abscess formation, in the patient with prolonged fever.

Serum electrolytes and arterial blood gas should be periodically monitored in the critically ill. Renal function tests monitoring is required as peripheral circulatory shock (due to septicaemia or myocarditis) and typhoid nephritis, can both lead to acute renal failure.

Bone marrow should be evaluated in patients with prolonged pancytopenia and for culture, when the diagnosis is in doubt. ADA (Adenosine deaminase enzyme) activity is raised in patients with Typhoid fever. However, it is not specific for Typhoid.

S. typhi produces changes in lipid profile. These changes return to normal only after a long time. Serum cholesterol, triglyceride and LDL cholesterol value decrease. Various theories including altered hormone levels due to gram-negative sepsis are responsible. It has no relation to mortality or morbidity.

D. BACTERIOPHAGE TYPING

In India, this task is performed by National Salmonella Phage Typing centre, Lady Hardinge Medical College, New Delhi. The phage typing schemes depends on the Vi-antigen of Salmonella typhi and makes use of the remarkable ability of Vi phage II to adapt to new host strains. Presently 106 phage types of *S.typhi* can be

identified and this is of great importance in epidemiological differentiation of organisms producing outbreaks, and for the identification of the source. The phage types which are most abundant and spread throughout the world are E1, A, B2, C1, D1 and F1. In India before 1990, phage type A was the commonest, but after 1990, phage type E1, became the commonest type.

MANAGEMENT[16,17]

Timely and appropriate management of a case of typhoid fever can substantially reduce the mortality and rate of complications.

GENERAL NURSING CARE AND DIET

General nursing care should be given due importance. General Hygiene should be maintained. Patient should be provided with 1500-1800 cal/day and fluid 2-3 lit / per day and electrolyte replacement. This high calorie diet increases patient's resistance to haemorrhage and perforation.

SPECIFIC ANTIMICROBIAL THERAPY

Since its introduction, chloramphenicol has been the antimicrobial gold standard for treatment of typhoid fever. The dose, oral or I.V. is 50 mg / kg body weight per day, about 4g/day. When the patient becomes afebrile, the dose is reduced to 30 mg / kg / day or 2g/day for 10 to 14 days.

Chloramphenicol

Chloramphenicol was the first drug to be used in the treatment of typhoid fever with unquestionable effectiveness. It acts by interfering with synthesis of bacterial proteins. It is essentially bacteriostatic. The original report on the effectiveness of Chloramphenicol in Typhoid fever was published by Woodward et al, in 1948. Since then chloramphenicol has remained the drug of choice in typhoid fever. A generally accepted regime is 50mg / kg / day in 3-4 divided doses till the patient is afebrile and afterwards 30 mg / kg /day for a period of not less than 14 days.

The 1st report of Chloramphenicol resistance was presented in 1950, in Britain. However subsequently, multiple drug resistant strains have been documented from Mexico, (where three was the 1st epidemic of resistant Typhoid in 1972) followed by India (Calicut), Thailand, Combodia, Vietnam and various parts of the world. Chloramphenicol resistance is plasmid mediated. Plasmids are transferred via coliforms to salmonella typhi. Plasmids mediated resistance is to multiple antibiotics including Ampicillin, Cotrimoxazole and Trimethoprim. Plasmids inactivate B lactamase and Chloramphenicol Acetyl transferase enzymes. The 2nd cause of resistance is the acquisition of a transferable extra-chromosomal resistance factor – "R" factor. Clinical and bacteriological relapse and carrier state is also common with Chloramphenicol therapy and its bone marrow toxicity is a serious drawback.

The problem is further complicated by the fact that in vitro sensitivity to the drug is not a reliable guide to the sensitivity of infecting organisms.

From Clinical view point, MDRST – multi drug resistant salmonella typhi, denote only those strains for which there is resistance to all three of the first line antibiotics (chloramphenicol, ampicillin and trimethoprim – sulfamethoxazole)

It is also evident that Quinolones have become the first drug of choice for the typhoid fever and there is also resistance to that drug due to its indiscriminate use and due to an altered DNA gyrase. Third generation cephalosproins are used in those resistant to quinolones.

Quinolones

They have reduced the 4 week long febrile illness to a short illness of few days, with relatively few complications and relapse and now emerged as the 1st line therapy in Typhoid fever [26]

The dosage schedules are as follows:

1. Ofloxacin in 400 mg / d for 7 to 14 days.
2. Pefloxacin in 400 mg / d for 7 to 14 days.
3. Ciprofloxacin 750 mg bid initially till the patient becomes afebrile then 500 mg bid for 7 to 14 days.
4. Norfloxacin (400 mg) 2 tab / bid till the patient becomes afebrile, then 400 mg bid for 7 to 14 days.

The duration of therapy is still under study and as short as 7 day therapy is mentioned but treatment should be continued till cultures are negative. These can be given orally or by I.V. infusion.

Third Generation Cephalosporines

Ceftriaxone, Cefotaxime, Ceftazidime, Cefixime, Cefpodoxime and Cefoperazone have been used in the treatment of Typhoid. Indications for use are as follows:

- Ciprofloxacin resistant typhoid
- Typhoid meningitis
- Typhoid in pregnancy and children <17 years
- G6PD deficiency
- Psychosis

Ampicillin / Amoxycillin

The dose of Ampicillin in Typhoid fever is 8g/day in adults or 200 mg / kg / day in children, given in divided doses. The dose of amoxicillin is 4-6g/day in adults and 100 mg/kg/day in children, given in 4 divided doses.

Aminoglycosides

Gentamycin and netilmicin are the 2 aminoglycosides used in typhoid fever. The dose of Gentamycin is 1-2mg/ kg, 8 hourly, or as a single dose 2 mg/kg/d; IM or if IV slowly over 20 to 30 min. to avoid neuromuscular toxicity. Netilmicin (along

with 3rd generation Cephalosporins) is considered as the drug of choice in *S. typhi* Meningitis. The dose of netilmicin used here is 500 to 750 mg bid for 14 days. However, effective short course chemotherapy of 7 days has also been described.

Role of Steriods[27,28]

Controlled trials using high doses of dexamethasone have focused attention once again on their value in selected cases with severe toxaemia, prolonged altered state of consciousness, shock and DIC, features known to carry a poor prognosis, Its use is based on the assumption that adrenocortical functions are impaired due to gram negative endotoxemia.

General Care

It includes fluid and electrolyte replacement. Hypokalemia, which can aggravate the paralytic ileus, should be corrected by intra-venous supplementation. The urine output should be monitored hourly. Blood transfusion in patients with hemorrhage, apt surgical intervention in patients with perforation, ionotropic support in shock, correction of hypoxia and continuous nasogastric suction for paralytic ileus, all play a major role in the complete management of the patient.

Treatment of Carriers[29,30]

Eradication of the chronic carrier state especially in the presence of Gall stones is notoriously difficult. Traditional regimens of 100 mg /d of Amoxycillin or Ampicillin with Probenecid 30mg/Kg/d; or Trimethoprim – Sulfamethoxazole

(!60/800 mg) twice a day plus Rifampicin 600 mg O.D. for at least 6 weeks, are all tried. Recent studies suggest that 4 weeks of treatment with quinolones gives better results. Prolongation of antimicrobial therapy for 3 months can cure some carriers with gallstones, however most reliable treatment is cholecystectomy plus antimicrobials. Quinolones are the best choice for chronic suppression of typhoid relapse in AIDS patients.

PREVENTION

Endemic Typhoid can be eliminated only by the provision of proper sanitation, a safe water supply and public health legislation designed to ensure uncontaminated food, drink and milk. Much work has been done on the preparation and evaluation of the efficacy of vaccines against typhoid since 100 years back. The credit for introducing typhoid vaccine goes to Sir Wright of Great Britain and Pfeiffer and Kolle of Germany. The first clinical trials were done by Wright on Soldiers of Indian army at the beginning of this century.

VACCINES

Vaccines Currently available

Three categories of vaccines are currently available against typhoid fever. These are:

- Parenteral killed whole cell vaccines , Heat and Phenol killed, Acetone killed and dried.

- Live attenuated Ty21a vaccine (TYPHORAL)
- Polysaccharide sub unit vaccine (TYPHIM Vi)

TAB Vaccine[31]

A modest degree of protection may be achieved by using either acetone killed or heat killed phenolysed TAB vaccine. The standard preparation contains *S.typhi* (1,000 million/ml), S. paratyphi A (500-750million/ml) and S. paratyphi B(500-750 million/ml) Primary immunisation consists of 2 dose of 0.5ml each given subcutaneously at an interval of 4-6 weeks. Booster doses are given every 3 years as immunity lasts only 3 years.

However, the TAB vaccine has fallen into disrepute due to the following reasons.

a. The paratyphoid antigens in the vaccine are not only thought to be of doubtful effectiveness, but their presence enhanced reactions caused by extra proteins of the Paratyphi A and B organisms, viz local pain, malaise, headache and pyrexia
b. Vaccination with TAB does not stimulate cell mediated immunity which is essential for protection.
c. The antibodies produced by TAB vaccination differs from that produced during the disease.

Hence WHO has recommended that the TAB vaccine should be discontinued.

The Vi capsular polysaccharide typhoid vaccine (Typhim VI)

The vaccine contains 25ucg of purified Vi capsular polysaccharide of *S. typhi* in each immunising dose. This vaccine, given intramuscularly, as a single dose, is supposed to give 80% protection for 3 years. However, the Vi antigen usually, but not invariably provides Vi antibody. Vaccination does not stimulate cell mediated immunity which is essential for protection, hence not of much benefit.

Ty21a oral Vaccine[32]

Oral vaccines lacking undesirable side effects have come up, of which Ty21a has emerged the best, after various clinical trials. Ty21a is a galactose epimerase mutant of *S.typhi* given as oral enteric coated capsules. The bacilli invade mononuclear cells and undergo 4-5 cell divisions in the intestinal tract. This stimulates immunity, but the bacilli do not survive within the cells, as they lack the essential enzyme UDP – galactose 0-4 epimerase and are therefore avirulent. The vaccine stimulates cell mediated immunity and also stimulate intestinal Ig A. Dose is 3 capsules, taken 1 on alternate day.

MDRST IN INDIA

MDRST was reported from India in early 1980s but the full impact was felt from 1989 onwards. From the published literature, it is evident that the proportion of MDRST between 1982-89 was about 13%, in 1990 it was about 50% and in next few years it increased to about 70-80%of the total *S.typhi* isolates. This data is hospital based and may not be representative of the true picture in the country. Prior to 1987

the resistance was reported only to chloramphenicol and tetracycline. In 1988 ampicillin got added to this list and from 1989 the resistance was reported to ampicillin, chloramphenicol, trimethoprim – sulfamethoxazole and tetracycline.

Because of the high incidence of MDRTF, the conventional antibiotics such as chloramphenicol, ampicillin, trimethoprim – sulfamethoxazole and tetracycline can no longer be considered as the first line drugs. Fluoroquinolones and third generation cephalosporins are the available therapeutic alternatives for treatment of MDRTF

To sum up there is an urgent need for epidemiological surveillance of MDRST isolates. There is also an urgent need to educate all health professional in the rational antibiotic therapy. The hospitals should have clear-cut antibiotic policy which should be periodically reviewed based on the changing antibiotic sensitivity patterns.

MATERIALS AND METHODS

This study was conducted in patients admitted to Coimbatore Medical College Hospital, Coimbatore during the period from January 2004 to December 2005.

Inclusion Criteria

For the purpose of this study the diagnosis of Typhoid Fever was clinically suspected when patients presented with a fever of more than 7 days duration, toxic look, coated tongue, Hepatosplenomegaly, relative bradycardia, not responding to treatment and also in the cases of pyrexia of unknown origin. Those with positive blood culture for salmonella were included in the study.

Exclusion Criteria

Those patients with negative blood culture for Salmonella were excluded from the study.

All these cases were examined in detail were investigated and followed up as per the proforma appended.

The blood culture and serological studies for typhoid were carried out as per standard techniques. Apart from the above, the routine urine, stool and haematological examination, skiagram of chest, abdomen , ECG were done according to the case needed.

Technique of Blood Culture

5 ml of Blood was collected aseptically in 50ml of bile broth and incubated at 37°c for 24 hours. Sub cultures were made on Macconkey medium or Blood agar plate, on days 2, 4, 8 and 15. Any non-lactose fermenting colonies were identified by standard technique and slide agglutination test. *S. typhi* appears as water drop like transparent colonies on Macconkey and grey white colonies on blood agar plate.

Technique of Widal test

5 ml of blood was collected aseptically and sent to the laboratory. The blood samples were allowed to clot at room temperature and sera separated aseptically. The clots were used for clot culture and serum was used for serology. The serum was centrifuged at 300 rpm for 10 minutes and clear supernatant was used. Widal test was carried out using standard methods with salmonella typhi O, Salmonella typhi H antigen.

The widal test was done during second week or 3rd week in the culture positive cases. In all the culture proved cases sensitivity was tested for chloamphenicol Ciprofloxacin, Cotrimoxazole, Cefotaxime and Ceftriaxone.

Treatment Schedule

All the patients with the positive culture were treated with appropriate antibiotics. According to the sensitivity, patients who were seriously ill were given the drugs parenterally or combined with steroids.

All the patients were discharged afebrile with advice for follow-up in case any febrile illness occurred. Follow up Blood, Urine and Stool culture were done after 3 months in these cases to detect carriers.

OBSERVATIONS

60 cases of culture proved typhoid fever were included in the analysis. Of these 32 were males and 28 were females. The age and sex distribution is given in table No.1

Table – 1

Age and Sex Distribution

Age(yrs)	Sex		Total
	Male	Female	
14 – 19	7	6	13
20 – 29	14	10	24
30 – 39	10	9	19
40, >40	1	3	4
Total	32	28	60

Table – 2

Monthly Distribution

Month	2004	2005
January	0	4
February	0	0
March	1	3
April	1	1
May	1	0
June	6	4
July	5	4
August	0	4
September	2	0
October	2	1
November	6	3
December	9	3
Total	33	27

Table No. 2 shows the monthly distribution of the adult cases from January 2004 to December 2005. Maximum numbers of cases were during June, July and November, December and January. But the seasonality remains throughout the year.

Epidemiological factors

1. *Social Class:*

   47 patients were from the poor class; many of them were living in crowded colonies. 10 cases were from middle class and 3 were students.

2. *Occupation:*

   43 patients were manual laborers. Students constitute 3, Housewives 14

3. *Food Habits:*

   All of them were taking mixed diet. The manual laborers and students used to take food from hotels at times. One patient acquired infection after his visit to Chennai. Two nursing students were living in hostel.

CLINICAL FEATURES

Symptoms

All the cases were presenting with history of fever varying from one week to three weeks duration. Headache was present in 42 cases. Abdominal pain was present in 35 cases vomiting was present in 32 cases. Diarrhoea was present in 10 cases (Table No. 3). Constipation was observed in 14 patients.

Table – 3

Symptoms

S. No.	Symptoms	No. of Cases	Percentage
1.	Fever	60	100%
2.	Headache	42	70%
3.	Vomiting	32	53%
4.	Constipation	14	23%
5.	Diarrhoea	10	16%
6.	Cough	20	33%
7.	Abdominal Pain	35	58%
8.	Jaundice	1	1.6%
9.	Urinary symptoms	6	10%

Respiratory symptoms in the form of cough, upper respiratory tract infections present in 16 cases and cough with sputum production in 8 cases. 1case presented with jaundice. Abdominal pain was observed in 35 cases. Urinary symptoms in the form of burning micturition was observed in 6 cases.

Table – 4

Signs

S. No.	Signs	No.of Cases	Percentage
1.	Pyrexia	60	100%
2.	Abdominal Tenderness	24	40%
3.	Abdominal Rigidity	6	10%
4.	Coated Tongue	38	63%
5.	Relative Bradycardia	6	10%
6.	Jaundice	1	1.6 %
7.	Hepatomegaly	30	50%
8.	Splenomegaly	35	58%

Signs

Fever was present in all the cases. The temperature varied from 99°F to 104°F. There was a fluctuation in the temperature pattern in the form of remittent in 9 and intermittent in 20, continuous fever in 31 and 11 had fever with chills and rigors. Relative bradycardia was observed in 6 cases. The central coating of the tongue with free margins was found in 38 cases.

Splenomegaly was noticed in 35 cases. The size varied from being tip palpable to 3.5 cms below left costal margin. The spleen was soft in consistency and tender in some cases. Hepatomegaly palpable from 1.5cm to 4cm below right costal margin was observed in 30 cases. Evidence of lobar pneumonia was present in one case. Abdominal tenderness was observed in 24 cases and abdominal rigidity found in 6 cases.

COMPLICATIONS

Table – 5

Complications of Typhoid Fever

S.No.	Complications or Atypical Presentation	No. of Cases
1.	Ileal Perforation	1
2.	Typhoid Meningitis	1
3.	Pneumonia	1
4.	Hepatitis	1
5.	Brodie’s abscess	0
6.	Typhoid Myocarditis	0

1 case presented with ileal perforation after a history of fever and acute abdomen Peritonitis was observed in that case and patient developed signs like acute appendicitis with absence bowel sounds. After surgery and treatment with appropriate antibiotics he improved.

One patient presented with symptoms of lobar pneumonia, not subsided with usual means of treatment and there was a persistent fever of 15 days with productive sputum of 200-300 ml / day. X ray revealed left basal pneumonia. *S. typhi* was isolated in culture, sensitive to ciprofloxacin and responded with that.

One case presented with history of 8 days fever, headache vomiting and signs of meningeal irritation. *S. typhi* was isolated in blood culture. CSF analysis showed non specific meningitis with CSF Neutrophil count of 12 cells / micro litre Glucose 60mg / dl and protein 80 mg / dl. and the patient improved clinically with cefatoxime.

1 patient had icterus with elevated bilirubin and SGOT, SGPT enzyme levels. They returned to normal after treatment with cefotaxime,

INVESTIGATIONS

Blood Cell Counts

Routine examination of the blood showed leucocyte counts varying from 3600-14,000 / cub.mm. In 14 cases the leukocytes count was between 10,000 and 14,000. In 12 cases the count was between 10,000 and 8,000 and in 24 cases the count

was between 8,000 and 4,500 in 10 cases the count was less than 4,500. Eosinophil count varied from 0-5%, other cell counts were within normal range.

Urine Examination

Albuminuria was seen in 1 case. Bile salts and bite pigments were present in 1 patient and haematuria in one patient.

Stool Examination

In one presented with diarrhoea naked eye examination of the stool showed blood and mucus, while microscopic examination showed RBC and Pus cells. No ova or cyst was found.

X-ray chest

Showed left basal pneumonitis in pneumonia patient, chronic bronchitis in one patient. It was normal in all other patients.

X-ray abdomen showed air under diaphragm in perforation case.

Biochemical Investigations

LFT : Abnormality in LFT was noticed in one patient. The serum bilirubin was 4 mg/dl in that patient with SGPT 210 U/L and SGOT 240 U/L. There were no change in level of alkaline phosphates and total protein and albumin and globulin .

Blood Urea: Blood Urea was elevated in the patient with perforation. Blood urea was 78 mg / dl and serum creatinine was 1 mg / dl in that case.

Bacteriological Culture and Serological Study

All the 60 cases which showed blood culture positive for *S.typhi* are included in the study. In these cases widal was positive in 46 cases (76%).

Follow up Blood, Urine, Stool Culture done after 3 months showed no growth in all these patients.

ANTI BIOTIC SENSITIVITY

Out of the 60 cases studied, 20 cases were sensitive to chloramphenicol, 18 cases were sensitive to cotrimoxazole, 56 cases were sensitive to ceftriaxone, 48 cases were sensitive to cefotaxime and 36 cases were sensitive to ciprofloxacin.

ANTIBIOTIC SENSITIVITY PATTERN

Chloramphenicol	Ciprofloxacin.	Cotrimoxazole	Cefotaxime	Ceftriaxone
R = 40 (67%)	R = 24 (40%)	R = 42 (70%)	R = 12 (20%)	R = 4 (7%)
S = 20 (33%)	S = 36 (60%)	S = 18 (30%)	S = 48 (80%)	S = 56 (93%)

DISCUSSION

The present study was undertaken to have an understanding of various aspects of typhoid fever as it occurs in the Coimbatore. 60 cases, included in this study had definite bacteriological support in which culture isolation for *S.typhi* was 100%.

Age- Sex incidence

In India most of the cases of typhoid fever occur in 5-39 age group. In our study only adults are included and the youngest patient was 14 year old. Maximum incidence is noted in the age group 14-29. 13 cases in the age group of 10-19 years. 24 cases in the age group 20-29 years, 19 cases in the age group of 30-39 years, 4 cases in the age group above 40 years.

Both sexes are equally susceptible 32 Male cases and 28 females cases were present in our study(1.14:1) The standard error of proportion (S.E=square root of pq/n) for this sample size of 60 is 6.45.S.E –Standard Error p-the expected proportion of males, q-the expected proportion of females n-the sample size. The observed difference is 4 (32-28) and it is less than twice that of standard error. Relative deviate=4/6.45=0.6,and is less than 2 and hence not significant

Ackers et al[33] reported male, female ratio of 1.27: 1 in their study. Hassan[34] reported male, female ratio of 1.3:1 in his study. .

Monthly Distribution

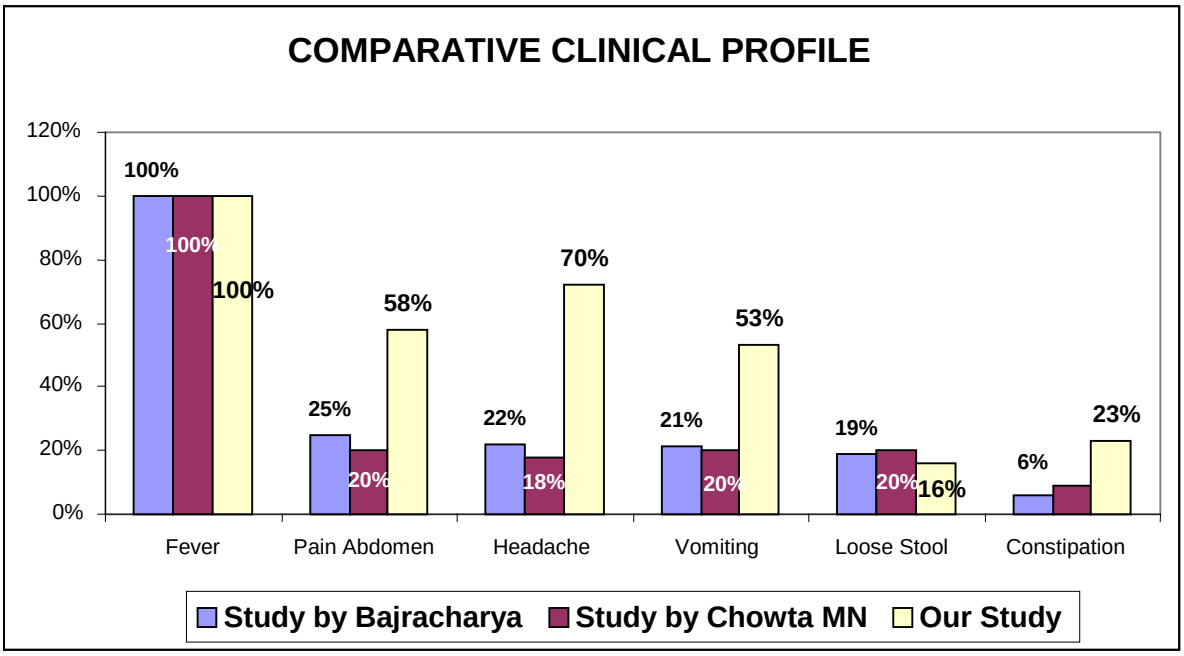
There is no seasonal variation in the countries where the disease is non-endemic. In our study peak incidence was noted during the period from June to August, November to January and the cases continue to occur throughout the year in Coimbatore.

CLINICAL MANIFESTATIONS

Table – 7

Frequency of Symptoms and Physical findings in patients with Typhoid Fever

Comparative Study	***Study by Ahmet Yeramis[35]***	***Study by Hassan[34]***	***Our Study***
Symptoms			
Fever	95%	100%	100%
Headache	38%	100%	70%
Vomiting	44%	30%	53%
Abdominal Pain	66%	71%	58%
Diarrhea	23%	22%	16%
Constipation	8%	20%	23%
Cough	15%	65%	33%
Physical Findings			
Fever	95%	100%	100%
Splenomegaly	20%	71%	58%
Hepatomegaly	42%	53%	50%
Relative Bradycardia	2%	40%	10%
Meningism	5%	-	1.6%



There are many objective data on the value of individual clinical symptom or sign in the diagnosis of typhoid fever in a febrile patient. The purpose of this study was to assess the value of some clinical and laboratory features in the diagnosis of typhoid fever.

Fever

Fever is present in all our patients, continuous fever in 51%, remittent in 15% intermittent in 34%.

100% is the reported incidence quoted in the study by Hassan[34]. Ahmet Yeramis[35] reported an incidence of 95% in his study. In a study conducted by Chowta

MN[36] in 2005 fever was shown to be present in 100% of the cases. In an another study by Bajracharya BL[37] in 2005 also fever was present in 100% of the cases.

Headache

In our study headache is present in 70% of the cases. In the study by Chowta MN, it was present in 18% of the cases and in the study by Bajracharya it was present in 22% of the cases. 38% of incidence is reported in study by Ahmet. 100% incidence reported in the study by Hassan.

Vomiting

Vomiting is present in 53% of our cases. It was present in 20% of the cases as per the study by Chowta MN and 21% in the study by Bajracharya, 30% is reported by Hassan. 44% is reported by Ahmet.

Abdominal Pain

Abdominal pain is present in 58% of our cases. It was present in 20% of cases in the study by Chowta MN, 25% of the cases in the study by Bajracharya and 66% as per the study by Ahmet. 71% is reported by Hassan.

Diarrheoa

Diarrheoa is present in 16% of our cases, it was present in 20% of cases in the study by Chowta MN and 19% in the study by Bajracharya, 23% as per the study by Ahmet.

Cough and Respiratory Symptoms

Cough and Respiratory Symptoms are present in 33% of our cases, they were present in 6% of case in the study by Chowta MN and 15% is the reported incidence in the study by Ahmet. 65% is reported by Hassan.

Urinary Symptoms

Burning micturition and frequence of micturition are present in 10% of our cases. They were present in 2% of cases in the study by Chowta MN.

Constipation

23% of our patients had constipation, 20% is reported by Hassan, 8% by Ahmet.

Splenomegaly

Splenomegaly is observed in 58% of our cases, 20% is the reported in the study by Ahmet. Arora R.K.[38] reported an incidence of 90% in his study. 71% is reported by Hassan.

Hepatomegaly

Hepatomegaly is present 50% of our cases, 42% is the reported incidence study by Ahmet. Hassan reported an incidence of 53%.

Relative Bradycardia

Relative bradycardia is present in 10% of cases in our study. Hassan reported 40% incidence of relative bradycardia in his study. 2% incidence is reported by Ahmet.

Tongue Coating

Tongue coating is present in 63% of cases in our study, it is present in 57% of cases in the study by Chowta MN and 62% of cases in the study by Bajracharya.

Rose Spots

None of our patients had rose spots. Ahmet reported an incidence of 1% in his study. Hassan reported 5% incidence.

INVESTIGATIONS

Blood Cell Counts

25% of our patients had leucocyte counts less than 4500 / micro litre. Leukopenia with counts less than 4500 / micro litre had been recorded in 18% of the patients by Ahmet et al. Mishra[39] reported 37% incidence of leucopenia in his study.

Widal Test

It is positive in 46 of our patients (76%). 80% positivity is reported by Hassan, 56% positivity is reported by Arora R.K.

COMPLICATIONS

Intestinal perforation

It was present in 1 of our 60 patients. It was present in 1.2% of the cases in the study conducted by Chowta MN. It was present in 1% of the cases in the study by Arora R.K et al. The perforation is most liable to occur at the lower end of ileum. Mortality rates are high. It is high in patients with late presentation, poor nutrition, very high or very low leucocyte count and when there has been a delay in the diagnosis and institution of treatment. It classically occurs in the 2nd week, but may occur earlier and also occurs in patients with relapse.

Perforation leads to complications like adhesions, obstruction and shock. Wedge resection, segmental resection or sealing of perforation (if small) are to be done in cases of perforation, bowel perforation was closed in 2 layers in our patient. Surgery should be done in the hands of any expert, as ileum is very fragile. Cases of perforation were often complicated by haemorrhage, peritonitis, shock and poor general condition of the patient, which account for poor prognosis. Metronidazole is to be added to antityphoid antibiotics in patients with perforation.

Neuropsychiatric Manifestations

One of our patient presented with meningitis. Meningitis or meningism is present in 5% of the cases in the study by Ahmet, 2.3% of the cases in the study by Arora RK. Neuropsychiatric Manifestations of typhoid are commonly encountered in the tropics. Usually the prognosis is good and the neuropsychiatric symptoms

disappear on treatment of typhoid. In our study meningitis patient improved without sequelae.

Hepatobiliary Complications

Hepatitis with bilirubin level of 4mg / dl, SGOT 240 U/l. and SGPT 210 U/l were seen in one of our patients. Hepatitis is present in 2.3% of the cases as per the study by Chowta MN.

Typhoid Pneumonia

It is seen in one of our patient. It is present in 3% of the cases in the study by Chowta MN and 1.7% in the study by Bajracharya. It occurs during the 2^{nd} and 3^{rd} week.

Myocarditis

None in our study showed features of myocarditis like cardiomegaly ST, T changes except sinus tachycardia. Myocarditis is present in 6% of the cases in study by Chowta MN.

Relapse in Typhoid Fever

Return of fever and symptoms of disease , culture of *S.typhi* positive in blood / stool and fever of more than 100°F, after full course of therapy constitute relapse cases. All our patients responded to treatment and became afebrile and none had relapse.

Carrier State

Follow-up blood, Urine and stool culture after 3 months in our patients showed no growth in all the cases. This confirms that full course of treatment with appropriate antibiotics as found by culture sensitivity makes carrier state unlikely.

ANTIBIOTIC SENSITIVITY

In our study 33% of the cases were sensitive to Chloramphenicol, 67% were resistant to Chloramphenicol. 60% of the cases were sensitive and 40% of the cases were resistant to Ciprofloxacin, 30% of the cases were sensitive and 70% of the cases were resistant to cotrimoxazole. 80% of the cases were sensitive and 20% of the cases were resistant to Cefotaxime. 93% of the cases were sensitive and 7% of the cases were resistant to Ceftriaxone.

In the study by Chowta MN 27% of the cases were sensitive and 73% of the cases were resistant to Amoxycillin , 36% of the cases were sensitive and 64% were resistant to Chloramphenicol, 46% of the cases were sensitive and 54% of the cases were resistant to Ampicillin, 36% of the cases were sensitive and 64% of the cases were resistant to Cotrimoxazole, 82% of the cases were sensitive and 18% of the cases were resistant to Ciprofloxacin, 100% of the cases were sensitive to 3rd Generation cephalosporins.

In the study by Bajracharya 100% of the cases were sensitive Ofloxacin, 9% were sensitive to Chloramphenicol, 12% were sensitive to Ciprofloxacin. In his study 3rd Generation cephalosporins alone were used in treatment, Cefixime in 33% of the cases, Ceftriaxone in 9% of the cases and Cefpodoxime in 9% of the cases. 6% of Cefixime and 3% of Ceftriaxone treated cases needed second line therapy as the defeverscent period was more the 6 days.

Mishra reported resistance to Chloramphenicol, Cotrimoxazole, Amoxycillin in 78%, 76% and 68% of patients respectively in his study.

In the study by Hassan 77% cases were sensitive to cefixime, 40% cases were sensitive to ciprofloxacin. 60%, 95%, 40% and 50% were the sensitivity to ceftriaxone, chloramphenicol, Ofloxacin and Ampicillin respectively.

Ahmet reported 100% sensitivity to quinolones and chloramphenicol. Deshmukh[40] reported 57% sensitivity to chloramphenicol.

CONCLUSION

60 cases of typhoid fever were studied with regard to clinical features, Complications, laboratory investigations and drug sensitivity pattern.

1. Typhoid fever occurs with slightly higher frequency in males which is not statistically significant, peak incidence has been shown to be in the 14 to 29 yrs age group. Peak incidence of cases were reported during November – January and also during rainy season, June – July probably because of monsoon and contamination of water. The most consistent features of typhoid in this study were fever, headache, vomiting, abdominal pain, coated tongue and splenomegaly. Fever need not be in the classical step ladder pattern, it may be continuous, remittent or intermittent.

   The white cell count appears to play little role in the diagnosis of typhoid fever, leukopenia is observed in only 25% of our patients. Diagnosis of typhoid fever is made by culture of S. typhi and the age old Widal test though lost its significance, still holds good. It is positive in 76% of our patients.

2. Intestinal perforation, meningitis, pneumonia and hepatitis are the complications encountered in this study. Ileal perforation has bad prognosis. Neuropsychiatric manifestations and hepatitis have good prognosis and they disappear on antibiotic treatment of typhoid fever. Full course of treatment with appropriate antibiotics as studied by culture and sensitivity makes carrier state unlikely as shown in our study.

3. Third generation cephalosporins and Quinolones are the drugs of choice in typhoid fever. Even though MDRTF is an outcoming problem in our country, 33% of the patients in our study were sensitive to chloramphenicol and all of them responded well clinically. None of the case showed chloramphenicol induced aplastic anaemia in our study. Thus Chloramphenicol may continue to play a role in the management of typhoid fever.

SUMMARY

Sixty cases of typhoid fever, proved by blood culture were studied during the period from January 2004 to December 2005 at Coimbatore Medical College Hospital, Coimbatore.

There were 32 males and 28 females in the study. The peak incidence is found to be in 14-29 age group, majority of cases occur during November to January and also in June and July months.

The consistent features of typhoid fever present in this study were fever (100%), headache (70%), vomiting (53%), abdominal pain (58%), coated tongue (63%) and splenomegaly (58%). WBC counts less than 4,500 cells / microlitre are seen in 25% of the cases. Widal test is positive in 76% of cases.

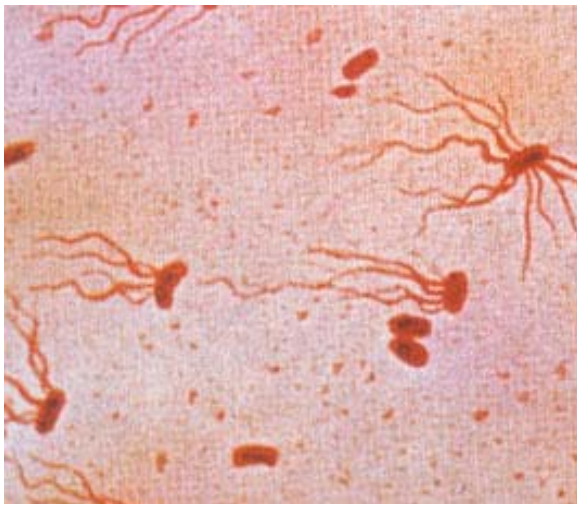
Out of 60 patients studied one had intestinal perforation, one had hepatitis, one had lobar pneumonia and one had aseptic meningitis. Follow up stool, blood and urine culture after three months showed no growth in the cases treated.

In blood culture and sensitivity 33% of cases were sensitive to chloramphenicol, 60% of the cases were sensitive to ciprofloxacin, 30% of the cases were sensitive to cotrimoxazole, 80% of the cases were sensitive to Cefotaxime and 93% of the cases were sensitive to ceftriaxone.

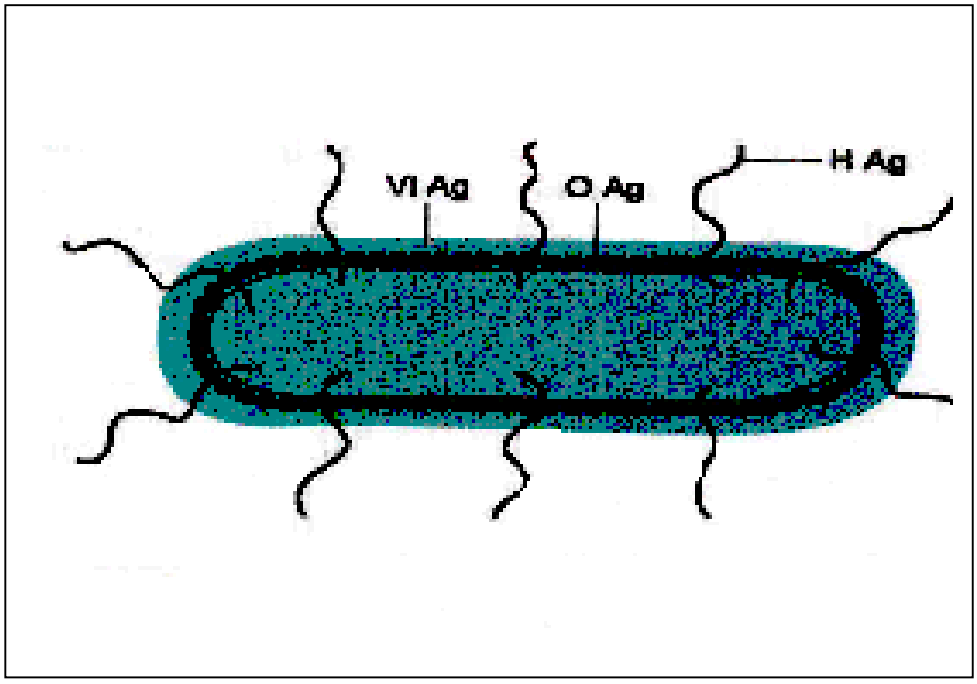
THE CAUSATIVE AGENT

Salmonella Typhi

***Salmonella Typhi,* Flagellar Stain**



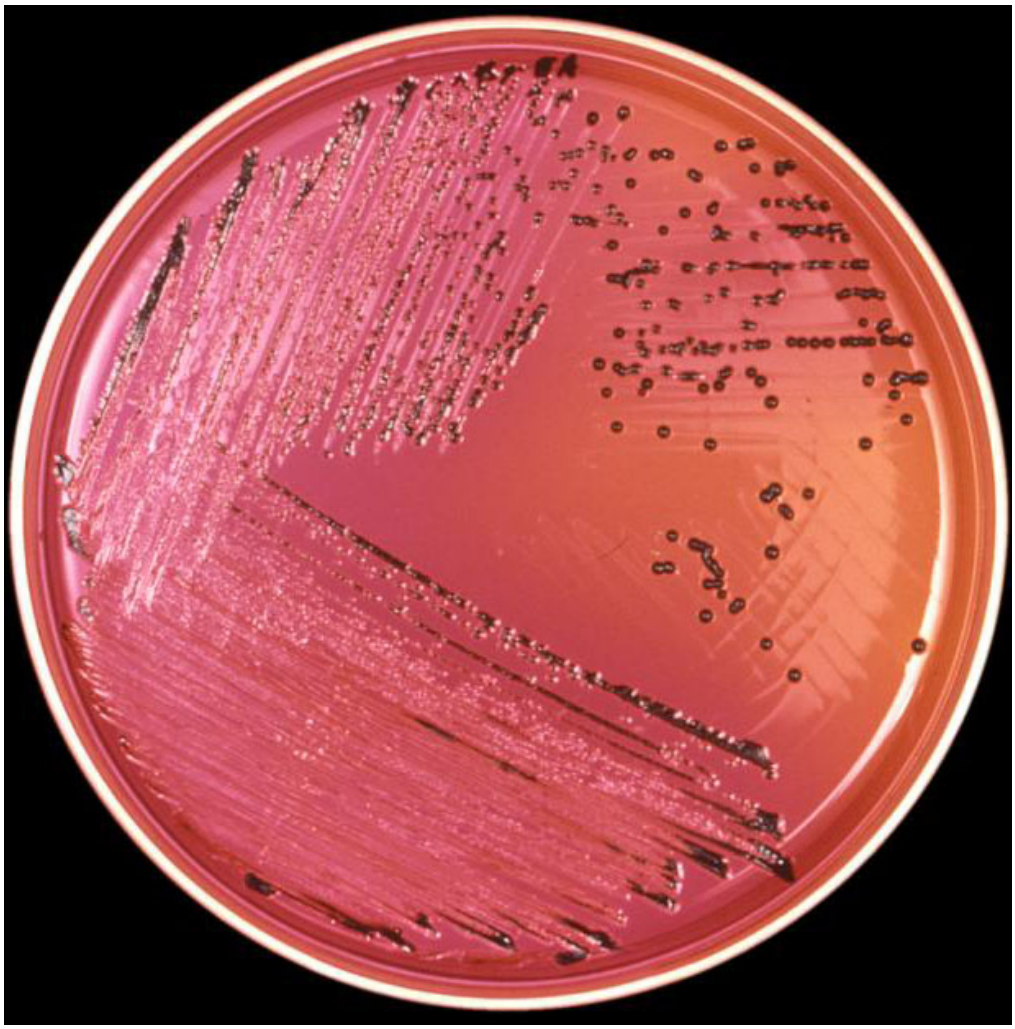
Antigenic structure of S. Typhi



Salmonella Typhi - Blood Culture
NLF Colonies

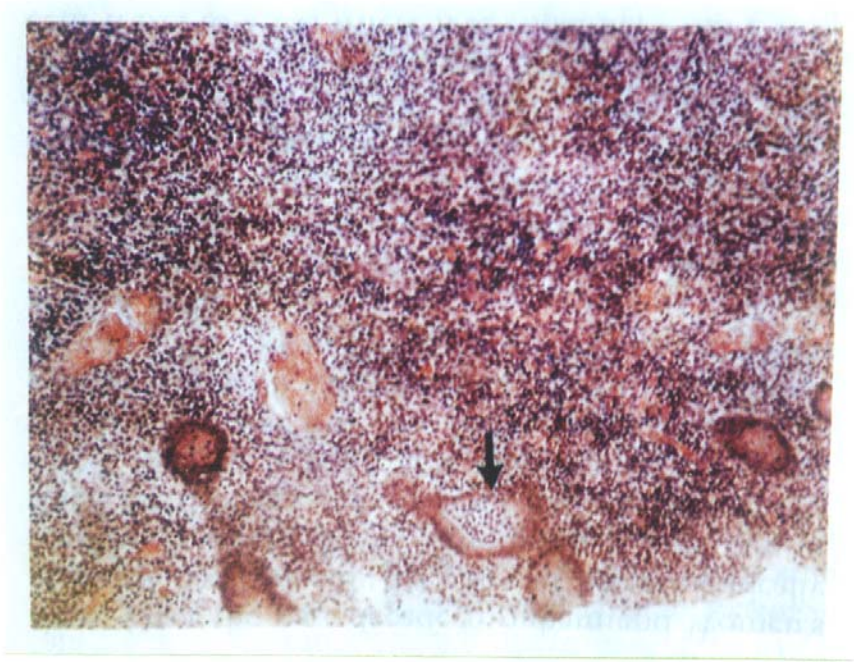
Salmonella Typhi – XLD Medium

(Xylose Lysine Deoxycholate)



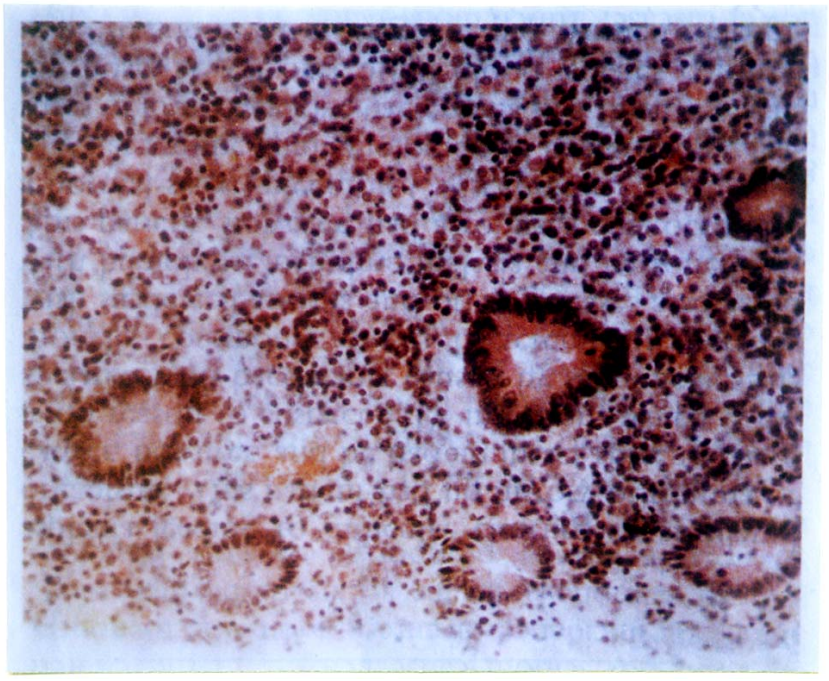
Active ileitis with Crypt Abscess and a Polymorphous infiltrate in the Lamina

(Hematoxylin and Eosin, X 45)

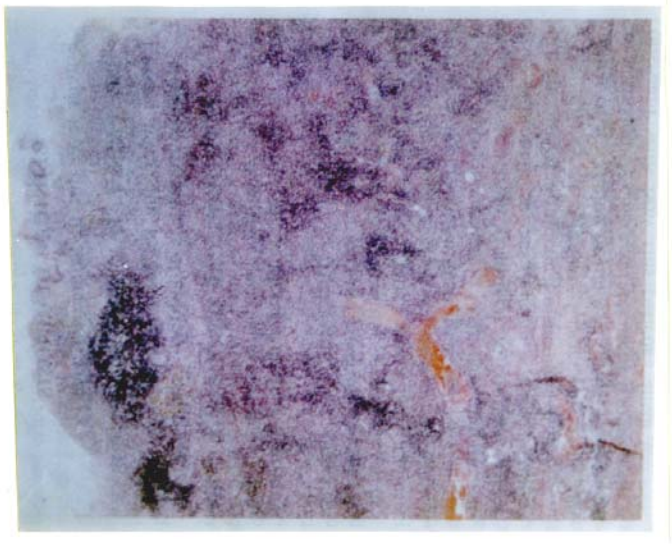


Infiltrate with Many Plasma Cells and Epithelioid Histiocytes

(Hematoxylin and Eosin X 90)

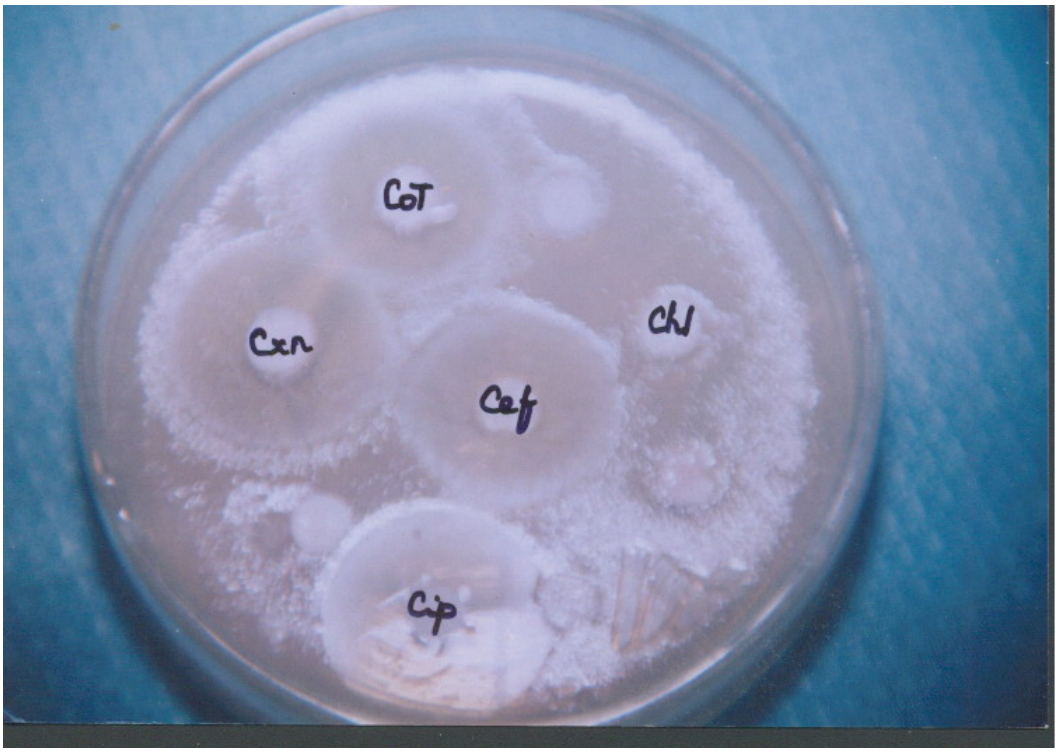


And Surface Ulceration (Haemotoxylin and Eosin, X 18)



Opened, Formalin – Fixed Specimenof Terminal Ileum
from patient with typhoid fever showing ulceration of Peyer's Patches

DRUG SENSITIVITY



CoT – Cotrimoxazole

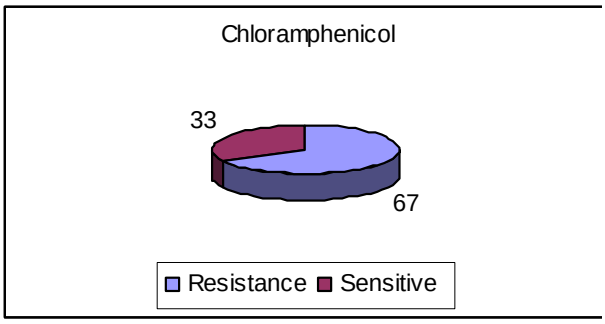
Cxn – Ceftrioxone

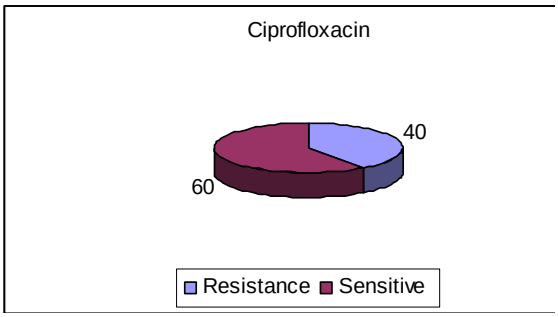
Cip – Ciprofloxacin

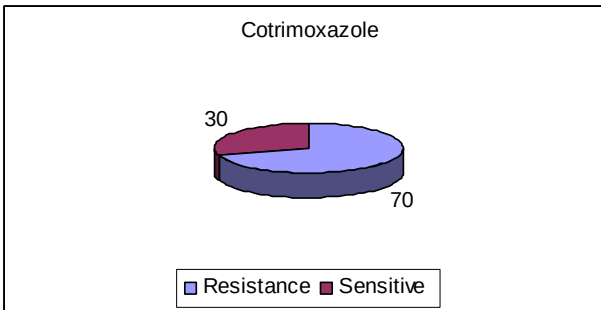
Chl – Chloramphenicol

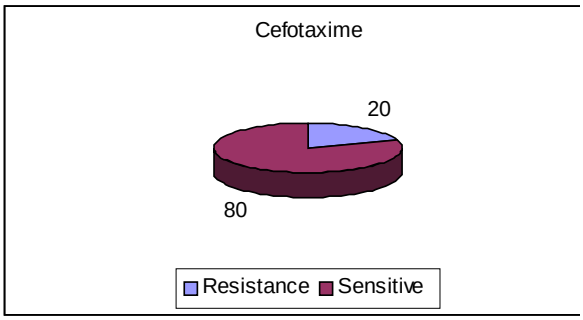
Cef - Cefotaxime

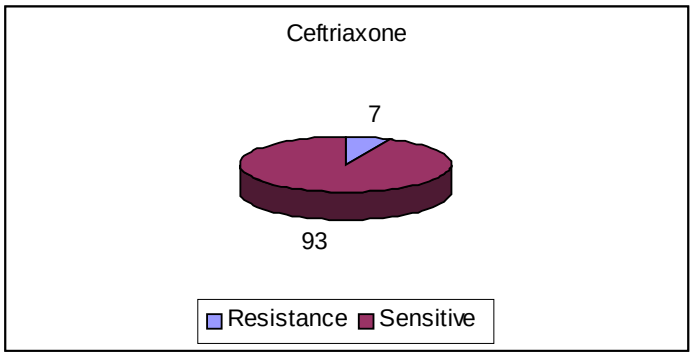
SENSITIVITY PATTERN IN OUR STUDY

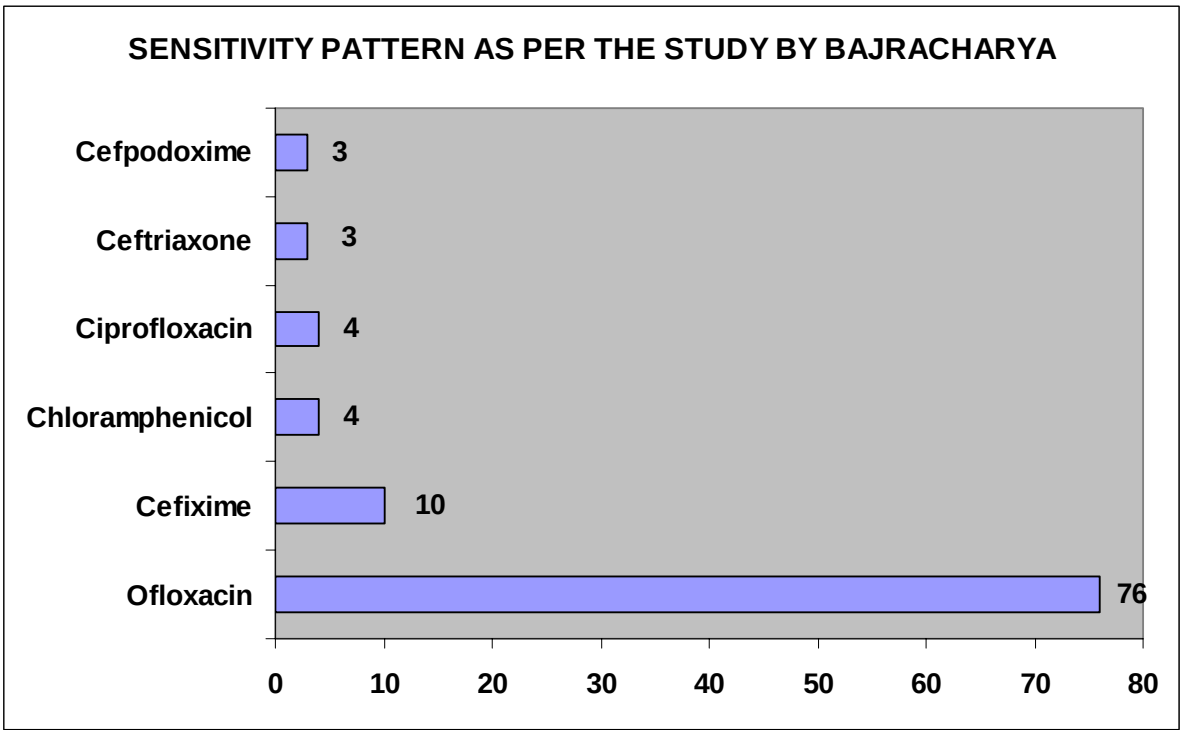


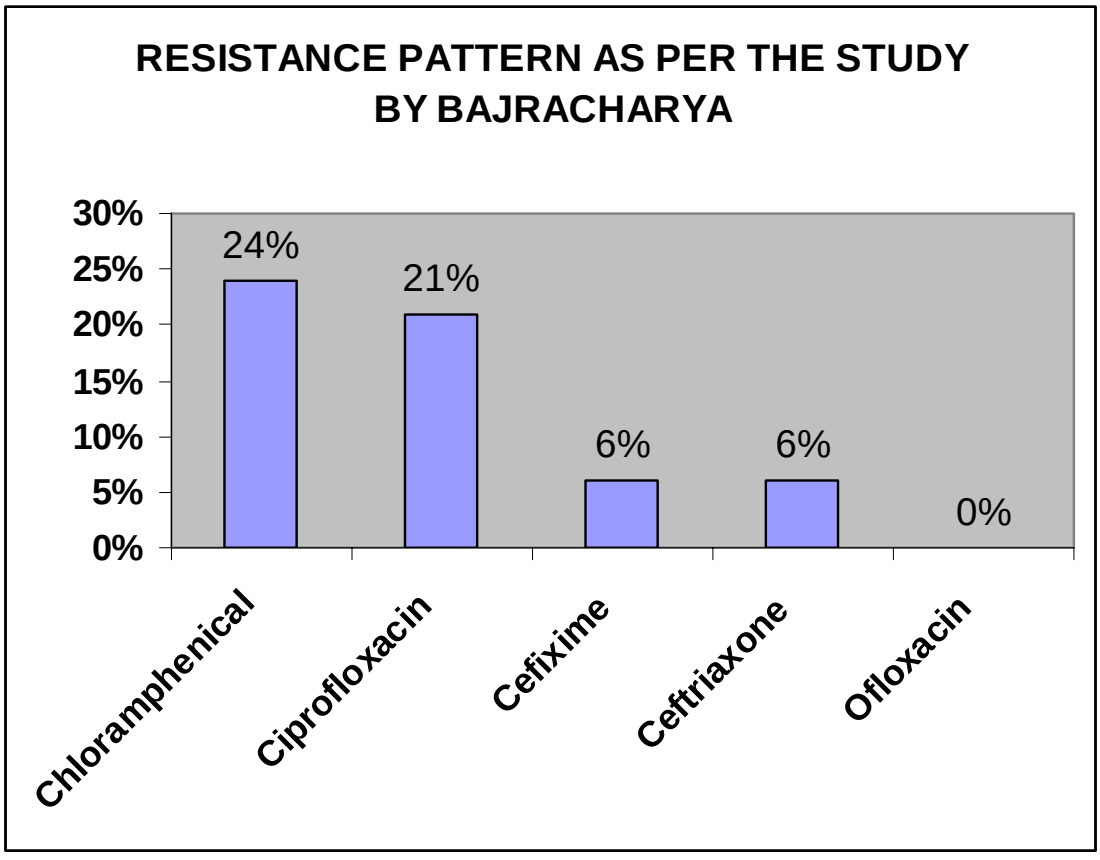









SENSITIVITY PATTERN AS PER THE STUDY BY BAJRACHARYA
Cefpodoxime
3
Ceftriaxone
3
Ciprofloxacin
4
Chloramphenicol
4
Cefixime
10
Ofloxacin
76
0
10
20
30
40
50
60
70
80


RESISTANCE PATTERN AS PER THE STUDY BY BAJRACHARYA
30%
25%
20%
15%
10%
5%
0%
24%
21%
6%
6%
0%
Chloramphenical
Ciprofloxacin
Cefixime
Ceftriaxone
Ofloxacin

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A HOSPITAL BASED SURVEY

PROFORMA

S. No.	I.P. No.	
Name :	Age :	Sex:
Address:	Occupation:	Income:
DOA :	DOD :	
Diagnosis		

SYMPTOMS:

General

- Fever — Duration
- Headache
- Vomiting
- Constipation

RESPIRATORY SYMPTOMS:

- Cough
- Expectoration
- Epistaxis

OTHERS:

HISTORY OF PAST ILLNESS:

HISTORY OF TYPHOID FEVER IN CLOSE CONTACTS:

HISTORY OF TYPHOID VACCINE:

FAMILY HISTORY:

PERSONAL HISTORY:

TREATMENT HISTORY:

Drugs used – dosage and duration

INVESTIGATION DONE BEFORE ADMISSION:

- Available verified
- Infered

PHYSICAL EXAMINATION:

General Examination

- Weight - On Admission
  - At Discharge
- Temperature Pattern

- Pulse rate Relative Bradycardia Present / Absent
- BP
- Rose Spots
- Others - Relevant - Not Relevant

ABDOMEN:

- Tenderness - Right Iliac Fossa
- Liver - Spleen

RESPIRATORY SYSTEM:

- Evidence of Bronchitis - Wheeze
  - Crackles

CARDIOVASCULAR SYSTEM:

- Evidence of Myocarditis
- Unrelated other findings

NERVOUS SYSTEM:

- Evidence of
  - Meningitis
  - Peripheral Neuropathy

INVESTIGATION:

Urine

- Protein
- Glucose
- Microscopic

Blood

- TLC
- DLC
- ESR
- Culture of Enteric Fever Organisms
- Widal
- Malarial Parasite

Clot Culture

Faeces Culture

- ECG
- XRAY

TREATMENT:

- Drugs used – dose and duration
- Completion of Drug Therapy

COMPLICATIONS DETAILS:

MASTER CHART

S.No.	Name	IP/OP No.	Age (yrs)	Sex	Previous H/O - enteric fever	Fever	Headache	Vomiting	Abdominal pain	Loose stools	Constipation	Cough	Urinary symptoms	Splenomegaly	Hepatomegaly	Tongue coating	Hepatitis	GI preforation	Pneumonia	Myocarditis	Meningitis	Blood Culture	Widal Test	Culture sensitivity					Follow up		
																								Chl	Cip	CoT	Cef	Cxn	Blood Culture	Faeces Culture	Urine Culture
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	19	20	21	22	23	24	25	26					27		
1	RANI	25615	14	F	A	P	P	A	P	A	A	P	A	P	P	A	A	A	A	A	A	s.typhi	O-100 H-100	R	S	R	S	S	NG	NG	NG
2	SHANTHI	26334	16	F	A	P	A	P	A	A	P	A	A	A	A	P	A	A	A	A	A	s.typhi	O-100 H-200	R	R	S	R	R	NG	NG	NG
3	AJINITHA	26354	19	F	A	P	P	P	P	A	A	A	A	P	A	A	A	A	A	A	A	s.typhi	O-Neg. H-100	R	S	R	S	S	NG	NG	NG
4	ANISHA	39102	15	F	A	P	P	A	P	A	P	P	A	P	A	P	A	A	A	A	A	s.typhi	O-200 H-400	S	S	R	S	S	NG	NG	NG
5	SINDHU	29106	15	F	A	P	P	P	P	A	A	A	P	A	P	P	A	A	A	A	A	s.typhi	O-200 H-200	R	S	R	S	S	NG	NG	NG
6	SELVI	29859	14	F	A	P	P	A	A	P	A	P	A	P	P	A	A	A	A	A	A	s.typhi	O-400 H-400	S	R	S	S	S	NG	NG	NG
7	KALAI	2879	22	F	P	P	P	P	P	A	A	A	A	P	A	P	A	A	A	A	A	s.typhi	O-200 H-400	R	S	R	S	S	NG	NG	NG
8	REKHA	30369	22	F	A	P	A	P	A	A	P	P	A	A	P	P	A	A	A	A	A	s.typhi	O-200 H-200	R	R	R	S	S	NG	NG	NG
9	RADHA	8456	23	F	A	P	P	P	P	A	A	A	A	P	P	A	A	A	A	A	A	s.typhi	O-100 H-400	S	S	S	S	S	NG	NG	NG
10	AMMU	8405	25	F	A	P	P	A	A	P	A	P	A	A	A	P	A	A	A	A	A	s.typhi	O-100 H-400	R	S	R	R	R	NG	NG	NG
11	ESWARI	31333	26	F	A	P	A	P	P	A	A	A	A	A	P	A	A	A	A	A	A	s.typhi	O-400 H-400	R	S	R	S	S	NG	NG	NG
12	DEVI	30218	23	F	A	P	P	P	P	A	P	P	A	P	A	P	A	A	A	A	A	s.typhi	O, H Neg	S	R	S	S	S	NG	NG	NG
13	LAKSHMI	3153	27	F	A	P	P	A	P	A	A	A	A	A	P	A	A	A	A	A	A	s.typhi	O, H Neg	R	S	R	R	S	NG	NG	NG
14	VIJAYA	8678	22	F	A	P	A	P	P	A	A	P	A	P	P	P	A	A	A	A	A	s.typhi	O, H Neg	R	R	R	R	R	NG	NG	NG
15	ANANDHI	8225	26	F	A	P	P	A	A	A	A	A	A	A	A	A	P	A	A	A	A	s.typhi	O, H Neg	S	S	S	S	S	NG	NG	NG
16	RAJI	9989	23	F	A	P	A	P	P	A	P	P	A	P	P	P	A	A	A	A	A	s.typhi	O-100 H-400	R	R	R	S	S	NG	NG	NG
17	PAVITHRA	9111	30	F	A	P	P	A	P	A	A	A	A	A	P	A	A	A	A	A	A	s.typhi	O, H Neg	R	S	R	S	S	NG	NG	NG
18	NISHA	32162	31	F	A	P	P	P	P	A	A	A	A	P	A	P	A	A	A	A	A	s.typhi	O-100 H-100	S	R	S	S	S	NG	NG	NG
19	MAHESWARI	36327	33	F	P	P	A	A	P	A	A	A	A	A	P	A	A	A	A	A	A	s.typhi	O-400 H-400	R	S	R	S	S	NG	NG	NG
20	POONGODI	578	32	F	A	P	P	P	P	A	A	A	A	P	P	P	A	A	A	A	A	s.typhi	O, H Neg	R	R	S	S	S	NG	NG	NG
21	PREETHA	32546	33	F	A	P	P	P	P	A	A	A	A	P	P	A	A	A	A	A	A	s.typhi	O-100 H-100	R	S	R	S	S	NG	NG	NG
22	DEEPIKA	33199	32	F	A	P	P	A	P	A	A	A	A	A	P	P	A	A	A	A	A	s.typhi	O-200	R	R	R	R	S	NG	NG	NG
23	MANIMEGALAI	2719	33	F	A	P	P	P	P	A	A	P	P	P	P	P	A	A	A	A	A	s.typhi	O-400 H-200	R	S	R	S	S	NG	NG	NG
24	LATHA	4448	34	F	A	P	P	A	P	A	A	A	A	P	A	A	A	A	A	A	A	s.typhi	O-100 H-200	S	S	R	S	S	NG	NG	NG
25	RAJESWARI	35757	33	F	A	P	P	P	A	A	A	P	P	P	A	P	A	A	A	A	A	s.typhi	O, H Neg	S	R	S	S	S	NG	NG	NG
26	DEEPA	5399	41	F	A	P	A	A	P	A	A	A	A	A	A	A	A	A	A	A	A	s.typhi	O-400 H-400	R	S	R	S	S	NG	NG	NG
27	SAVITHRI	4609	41	F	A	P	P	A	A	A	P	A	P	A	P	A	A	A	A	A	A	s.typhi	O, H Neg	R	S	S	R	S	NG	NG	NG
28	NAYAGI	6996	40	F	A	P	P	P	P	A	A	A	A	P	A	P	A	A	A	A	A	s.typhi	O-100 H-200	R	R	R	S	S	NG	NG	NG
29	GOWTHAM	2290	14	M	A	P	A	A	A	P	A	A	A	P	A	A	A	A	A	A	A	s.typhi	O-400 H-400	S	S	R	R	S	NG	NG	NG
30	CHANDRAN	36827	15	M	A	P	P	P	A	A	A	P	A	A	P	P	A	A	A	A	A	s.typhi	O, H Neg	R	R	S	S	S	NG	NG	NG

M : MALE F. FEMALE A: ABSENT P: PRESENT R: RESISTANT S : SENSITIVE NG : NO GROWTH
CHL: CHLORAMPHENICOL CIP: CIPROFLOXACIN COT: COTRIMOXAZOLE CEF : CEFOTAXIME CXN : CEFTRIAXONE

MASTER CHART

S.No.	Name	IP/OP No.	Age (yrs)	Sex	Previous H/O - enteric fever	Fever	Headache	Vomiting	Abdominal pain	Loose stools	Constipation	Cough	Urinary symptoms	Splenomegaly	Hepatomegaly	Tongue coating	Hepatitis	GI preforation	Pneumonia	Myocarditis	Meningitis	Blood Culture	Widal Test	Culture sensitivity					Follow up		
																								Chl	Cip	CoT	Cef	Cxn	Blood Culture	Faeces Culture	Urine Culture
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	19	20	21	22	23	24	25	26					27		
31	SUBRAMANI	8323	16	M	A	P	P	A	A	A	A	A	A	P	P	P	A	A	A	A	A	S.typhi	O-400 H-400	R	S	R	R	S	NG	NG	NG
32	ARUMUGM	36872	19	M	A	P	A	P	P	A	P	A	A	A	P	A	A	A	A	A	A	S.typhi	O, H Neg	S	R	S	S	S	NG	NG	NG
33	PALANIAPPAN	11413	17	M	A	P	P	A	A	A	A	A	A	P	A	P	A	A	A	A	A	S.typhi	O-200 H-100	R	S	R	S	S	NG	NG	NG
34	PURUSHOTHAMAN	37650	18	M	A	P	A	A	P	A	A	A	A	A	P	A	A	A	A	A	A	S.typhi	O-100 H 50	S	R	S	S	S	NG	NG	NG
35	PASUPATHI	7442	19	M	A	P	A	A	P	A	A	A	A	P	A	P	A	P	A	A	A	S.typhi	O-50 H-50	R	S	R	S	S	NG	NG	NG
36	SUBBU	36455	21	M	A	P	P	P	A	P	A	A	A	A	P	A	A	A	A	A	A	S.typhi	O, H Neg	R	S	S	S	S	NG	NG	NG
37	RAVI	9534	22	M	A	P	P	P	P	A	P	A	A	P	A	P	A	A	A	A	A	S.typhi	O-25 H-25	S	R	R	S	S	NG	NG	NG
38	KUMAR	38296	25	M	A	P	A	A	A	A	A	A	A	A	P	P	A	A	A	A	A	S.typhi	O-50 H-100	R	S	S	S	S	NG	NG	NG
39	SUNDARAJAN	39504	26	M	A	P	P	P	P	A	A	A	A	A	A	P	A	A	A	A	A	S.typhi	O-100 H-100	R	S	R	S	S	NG	NG	NG
40	SAFI	39661	28	M	A	P	P	A	A	P	P	A	A	P	P	A	A	A	A	A	A	S.typhi	O, H Neg	R	S	R	S	S	NG	NG	NG
41	RAMKUMAR	2233	26	M	A	P	P	P	P	A	A	A	A	A	A	P	A	A	A	A	A	S.typhi	O-100 H-100	S	R	R	S	S	NG	NG	NG
42	MOHAN	7981	23	M	A	P	A	A	A	A	A	A	A	P	A	A	A	A	A	A	A	S.typhi	O, H Neg	R	S	R	S	S	NG	NG	NG
43	KARTHICK	39978	23	M	A	P	P	P	A	A	P	A	A	P	A	P	A	A	A	A	A	S.typhi	O-100 H-100	R	S	R	R	S	NG	NG	NG
44	VELUMANI	41113	24	M	A	P	P	P	P	A	A	A	A	P	P	P	A	A	A	A	A	S.typhi	O-100 H-50	R	S	R	S	S	NG	NG	NG
45	RAJAGOPAL	4280	25	M	A	P	A	A	P	A	A	P	A	P	A	P	A	A	A	A	A	S.typhi	O-100 H-200	S	R	R	S	S	NG	NG	NG
46	ARUNRAJ	5040	23	M	A	P	P	P	A	A	P	A	A	A	A	A	A	A	A	A	A	S.typhi	O-400 H-200	R	R	S	S	S	NG	NG	NG
47	DHARANI	5218	22	M	A	P	P	A	P	P	A	P	P	P	A	P	A	A	A	A	A	S.typhi	O-200 H-200	R	S	R	S	S	NG	NG	NG
48	SANTHOSH	46069	23	M	A	P	A	A	A	A	A	P	A	A	P	A	A	A	A	A	P	S.typhi	O-100 H-100	R	S	R	S	S	NG	NG	NG
49	SHANMUGAM	9701	28	M	A	P	P	A	P	A	P	A	A	A	A	P	A	A	A	A	A	S.typhi	O, H Neg	S	R	S	S	S	NG	NG	NG
50	SUNDARAM	9401	31	M	A	P	A	P	A	P	A	P	A	P	P	P	A	A	P	A	A	S.typhi	O-100 H-100	R	S	R	S	S	NG	NG	NG
51	RAJU	1146	38	M	A	P	P	P	P	A	A	A	A	A	A	P	A	A	A	A	A	S.typhi	O-100 H-400	S	R	R	S	S	NG	NG	NG
52	MURALI	44142	34	M	A	P	A	A	A	A	P	P	P	P	A	P	A	A	A	A	A	S.typhi	O-100 H-200	R	S	R	S	S	NG	NG	NG
53	SEKAR	591	36	M	A	P	P	P	A	P	A	A	A	P	P	A	A	A	A	A	A	S.typhi	O-100 H-100	R	R	R	S	S	NG	NG	NG
54	SANKAR	912	35	M	A	P	P	P	A	A	A	P	A	A	A	P	A	A	A	A	A	S.typhi	O, H Neg	S	R	S	S	S	NG	NG	NG
55	SELVARAJ	46085	36	M	A	P	A	A	P	P	A	A	P	P	P	P	A	A	A	A	A	S.typhi	O-400 H-400	R	S	R	R	R	NG	NG	NG
56	ANDAVAR	6266	33	M	A	P	P	P	A	A	P	A	A	P	A	P	A	A	A	A	A	S.typhi	O-200 H-400	S	S	R	R	S	NG	NG	NG
57	KARINKUMAR	47643	32	M	A	P	P	A	A	P	A	P	A	A	P	P	A	A	A	A	A	S.typhi	O-200 H-400	R	R	R	S	S	NG	NG	NG
58	HAKKIM	47688	33	M	A	P	P	P	P	A	A	A	A	P	P	P	A	A	A	A	A	S.typhi	O-100 H-100	S	R	S	R	S	NG	NG	NG
59	NAGAPPAN	36942	31	M	A	P	P	A	A	A	A	P	A	P	A	P	A	A	A	A	A	S.typhi	O-200 H-200	R	S	R	S	S	NG	NG	NG
60	RAMASAMY	27891	41	M	A	P	P	P	P	A	A	P	A	P	A	P	A	A	A	A	A	S.typhi	O-100 H-100	S	S	R	S	S	NG	NG	NG

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